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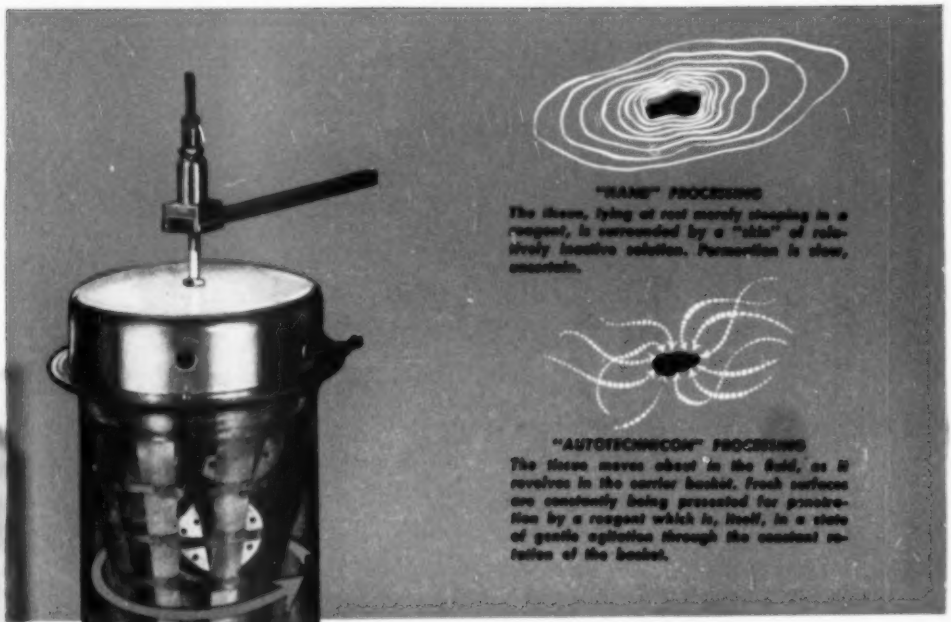
TABLE OF CONTENTS FIRST PAGE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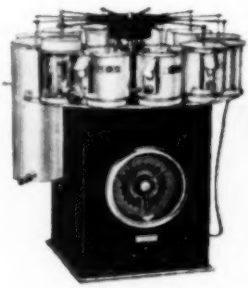

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CONTENTS

Original Articles

PAGE

Osteoma, Ossifying Fibroma, and Fibrous Dysplasia of Facial and Cranial Bones

Albert G. Smith, M.D., and Anibal Zavaleta, M.D., Durham, N. C. 507

Hyaline Material with Staining Reaction of Fibrinoid in Renal Lesions in Diabetes Mellitus

Leopold G. Koss, M.D., New York 528

Vitamin A Deficiency in the Duck

S. Burt Wolbach, M.D., and D. Mark Hegsted, Ph.D., Boston 548

Peliosis Hepatis

Frank T. Hamilton, M.D., Omaha, and Joseph M. Lubitz, M.D., Wood, Wis. 564

Arteriosclerosis in the Dog

Stuart Lindsay, M.D.; H. Feinberg, Ph.D.; I. L. Chaikoff, M.D.; C. Entenman, Ph.D., and F. L. Reichert, M.D., San Francisco 573

Regular Departments

News and Comment 592

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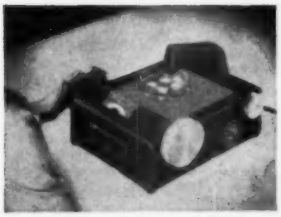

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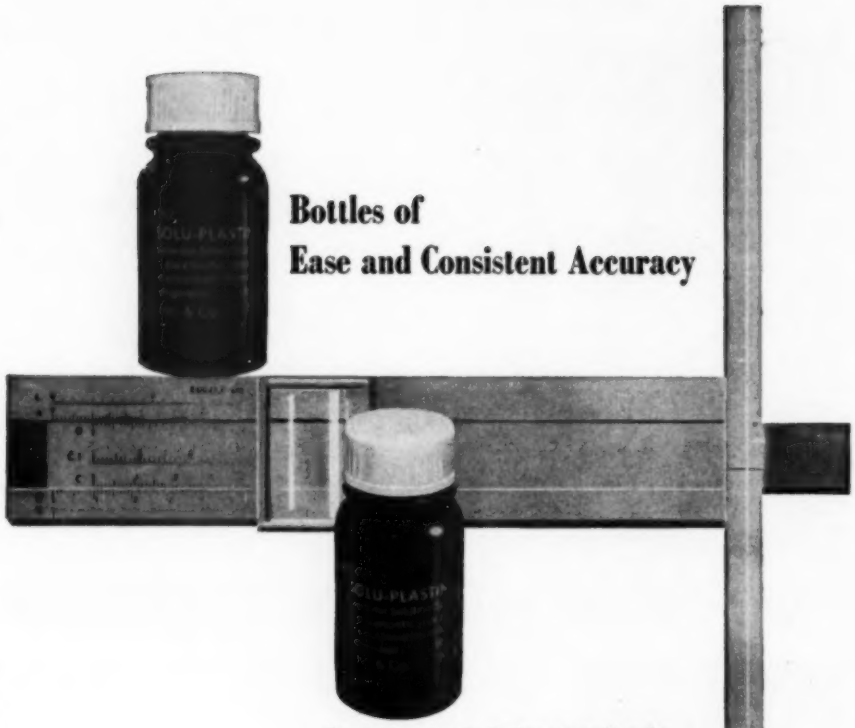

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OSTEOMA, OSSIFYING FIBROMA, AND FIBROUS DYSPLASIA OF FACIAL AND CRANIAL BONES

ALBERT G. SMITH, M.D.
AND
ANIBAL ZAVALETA, M.D.
DURHAM, N. C.

OSTEOMA is an intriguingly ambiguous term. It may be applied solely to eburnated bony lesions arising from membranous bones or it may include myositis ossificans and heterotopic bone lesions. It encompasses interesting fibrous variants of facial and cranial bone lesions, for example, monostotic fibrous dysplasia, or ossifying fibroma. These gritty, fibrous variants may be merged into obscurity by this inclusion and evaluation as osteomas, but it is the present tendency to regard them separately as fibrous dysplasia, a view championed by Schlumberger [1] and supported by Jaffe.[2] This view involves identification with a generalized bone disorder which may involve any bone and which is not considered as having a direct relation to osteoma. Clearly, this concept separates monostotic fibrous dysplasia of facial and cranial bones by schism from the old, all-inclusive class, osteoma. A somewhat separate line of reasoning is that monostotic fibrous dysplasia of facial or cranial bones and osteomas should be considered as related; that monostotic fibrous dysplasia may, when seen, bear no apparent relation to osteoma and that some facial osteomas may give no apparent evidence of origin from monostotic fibrous dysplasia, but that evidence does exist that some apparently completely ossified tumors in adults are the end-results of previous fibrous dysplastic processes and that the histologic line of distinction between the osteoma and dysplasia is purely arbitrary, one type grading into the other. In line with this reasoning, we believe that the designation "ossifying fibroma" as used by Geschickter [3] or "fibrous osteoma" as used by Phemister and Grimson [4] is justifiably used to demarcate this lesion from the main body of fibrous dysplasia. In brief, is it practical to postulate a separate category for a bony lesion of the face or cranium depending on whether it originated by ossification from osteoblasts or osteoblast-like cells in fibrous dysplastic lesions, called "sclerosed monostotic fibrous dysplasia," or originated by ossification without an apparent intervening fibrous phase, called "osteoma"? We

From the Department of Pathology, Duke University School of Medicine.

1. Schlumberger, H. G.: Fibrous Dysplasia of Single Bones (Monostotic Fibrous Dysplasia), Mil. Surgeon **99**:504, 1946.

2. Jaffe, H. L.: Fibrous Dysplasia of Bone, Bull. New York Acad. Med. **22**:588, 1946.

3. Geschickter, C. F., and Copeland, M. M.: Tumors of Bone, Ed. 3, Philadelphia, J. B. Lippincott Company, 1949.

4. Phemister, D. B., and Grimson, K. S.: Fibrous Osteoma of the Jaws, Ann. Surg. **105**:564, 1937.

believe it is not practical to separate these lesions completely in thought, although the use of separate terms can rightly depend on individual taste. Our beliefs are based upon conclusions gained from the following review of the examples of facial and cranial bone lesions to be found in the Duke Hospital files.

MATERIALS AND CASE DATA

The cases of ossifying fibromas (monostotic fibrous dysplasia) and osteomas of cranial and facial bones under review total 40. They are summarized in Table 1. They represent the ossifying fibromas and osteomas found among 176,000 surgical specimens processed in the last 20 years by the Department of Pathology of Duke University School of Medicine. They were chiefly from patients treated in Duke Hospital or its outpatient clinics, but some were from material referred to this

Fig. 1.—A striking ossifying fibroma of the right maxilla (Case 10, Table 1).

department by other North Carolina hospitals. Duke Hospital is a general hospital of 524 beds, and during the period included in this survey 438,840 patients were admitted to the hospital or examined in the clinics. The figures represent an incidence of 1 case of a facial or cranial bone lesion to approximately 10,000 admissions to the hospital or clinics, all outside cases being excluded. This incidence would be somewhat high for most general hospitals, and is due to the active plastic surgical, neurosurgical, and otolaryngological departments at this hospital.

The incidence of these bone lesions in the various sinuses in a study of 458 cases by Novick [5] was 39% in the frontal sinus, 24% in the ethmoid, 9% in the maxillary sinuses, and 1 to 2% in the sphenoid sinuses. In a series of this type there has in the past been no attempt to separate osteomas from ossifying fibromas.

Pathologic Anatomy.—The gross appearance of ossifying fibromas depends in part on the amount of surgical distortion, as in some instances only gritty, fibrous, yielding yet firm tissue fragments are available for examination. The complete

5. Novick, J. N.: Osteoma of the Frontal Sinuses, Arch. Otolaryng. **46**:655, 1947.

TABLE 1.—*Clinical Data*

Case No.	Duke Hosp. No.	Pathologic Diagnosis	Age, Race, Sex	Bone Involved	Clinical and X-Ray Appearance	Operation	Recurrence	Notes
1	A 70504	Ossifying fibroma, young	4 N F	R. maxilla and sinus	X-ray: hazy density of R. antrum displacing upper teeth; mass observable clinically	Weber incision, radical resection of tumor, with subtotal resection of upper jaw	None at 6 mo. postoperatively	Tumor first noticed 10 mo. prior to operation and thought to grow slowly thereafter
2	A 73080	Ossifying fibroma, young	6 W F	R. maxilla and sinus	X-ray: pressure thinning of neighboring structures; mass x-ray permeable; mass observable clinically	Intraoral approach, removal of well-encapsulated soft gritty mass	None at 3 mo. postoperatively	Tumor first noted 6 wk. prior to operation
3	A 20561	Ossifying fibroma, young to intermediate	19 N F	L. frontal bone and sinus, L. ethmoid	X-ray: cloudiness of L. frontal sinus and sphenoid sinus, destruction of ethmoid; clinical: swelling of L. frontal region with displacement of eye	Radical removal of partially encapsulated L. frontal-sinus mass; tumor destroying roof of orbit, ethmoids, and roof of mouth	None at 1 yr. postoperatively	Tumor noted 2 yr. prior to operation, with rapid, painless growth just prior to operation; L. nasal obstruction; menarche at 14; blood Ca and P normal
4	A 58119	Ossifying fibroma, young to intermediate	15 N F	L. maxilla and sinus	X-ray: haziness of maxilla, antrum, and zygomatic process	Ferguson incision with removal of encapsulated tumor fixed to maxilla	None at 1 yr. postoperatively	Painless growth for 4 mo. prior to operation; x-ray treatment 3 mo. prior to operation
5	76304	Ossifying fibroma, intermediate	24 N M	R. mandible	X-ray: cystic mass involving entire body of mandible, with opaque "spicules" through cystic area	Submucosal approach, firm, encapsulated 5 × 5 × 4 cm. nodular mass removed	.....	Tumor present at least 2 yr. prior to operation
6	94218	Ossifying fibroma, intermediate	27 N F	R. mandible	X-ray: 4 cm. expansible lesion in malar region; clinical: 4-5 cm. nontender mass firmly attached to bone	Radical removal of bony encapsulated tumor and ramus of right mandible	.....	Tumor noticed 1 yr. prior to operation; continued growing
7	A 17001	Ossifying fibroma, intermediate	17 N M	L. maxilla	X-ray: cystic area in L. upper-canine area and hard palate; clinical: 3 × 4 cm. mass, teeth normal	Area curetted and marsupialized	None at 3 mo.	.....
8	A 31702	Ossifying fibroma, intermediate	29 N M	R. mandible	X-ray: expansible osteolytic lesion of almost entire R. mandible, "basket weave" appearance	Resection of entire R. mandible with insertion of vitallium® plate; postoperative abscess, cleared; removal of plate 2 yr. postoperatively	None at 5 yr.	Mass noted 2 yr. prior to operation; growing, painless, loosened teeth; 5 yr. postoperatively new bone filled in mandible
9	A 35510	Ossifying fibroma, intermediate	10 W F	L. maxilla	X-ray: cloudiness of L. antrum, L. wing of sphenoid alveolar ridge, and sella turcica	Caldwell-Luc operation with partial resection of antrum tumor at age 10 and 4 yr. later of recurrent tumor	Tumor recurred and resected 4 yr. after 1st operation	Mass in left cheek since age 4; patient sent to surgeon by dentist
10	A 39905	Ossifying fibroma, intermediate	16 W F	R. maxilla	X-ray: tumor filling R. antrum and floor of orbit; clinical: tremendous tumor with local deformity	Radical resection of roof of mouth, ethmoid, zygoma, floor of orbit, and maxilla	None 3 yr. postoperatively	Tumor noted 2 yr. prior to operation (age 14); menarche at 15; heat treatments and 26 x-ray treatments prior to operation
11	A 46722	Ossifying fibroma, intermediate	26 W F	R. orbit	X-ray: enlargement and clouding of sphenoid sinus, retrobulbar tumor, haziness of R. mastoid	R. frontal craniotomy with removal of retro-ocular tumor invading roof of orbit, antrum, and sphenoid sinus	None 1 yr. postoperatively	1 yr. prior to operation, attack of blindness followed by exophthalmos, ophthalmoplegia, and blindness; menarche at 16
12	A 54260	Ossifying fibroma, intermediate	17 W F	Ethmoids	Clinical: mass at medial portion of orbit	Incision around medial part of eye with removal of orbit and ethmoid lesion by curette	None 20 mo. later	Painless swelling along medial canthus of left eye for 1 yr.

TABLE 1.—*(Continued)*

Case No.	Duke Hosp. No.	Pathologic Diagnosis	Age, Race, Sex	Bone Involved	Clinical and X-Ray Appearance	Operation	Recurrence	Notes
13	63510	Ossifying fibroma, mature	23 N M	R. mandible	X-ray: extensive osteoplastic process of body of R. mandible from 2d bicuspid to 3d molar, "sunburst" appearance with new bone formation; clinical: 4 × 4 cm. painless mass attached to mandible and soft tissues	Resection of R. body of mandible and portion of floor of mouth; ligation of external carotid	Patient died postoperatively from hemorrhage	Molar tooth extracted 10 mo. prior to operation; swelling of R. mandible noted 6 mo. prior to operation
14	A 809	Ossifying fibroma, mature	43 W F	R. frontal sinus	X-ray: slight density in region of R. frontal sinus	Eyebrow incision; anterior sinus plate and osteoma removed	None 2 mo. postoperatively	Pain and swelling in region of R. frontal sinus 18 mo. prior to operation
15	A 29483 and A 44568	Ossifying fibroma, mature	5 W F	L. maxilla	X-ray: density in maxillary sinus with displacement of teeth and floor of orbit	Alveolar ridge incision with partial resection of maxilla	Tumor recurred 3 yr. later (age 8); radical removal; recurred, age 10, no action	Trauma to alveolar ridge 2 yr. prior to development of lesion
16	A 29139	Ossifying fibroma, mature	11 W F	Skull	X-ray: expansive lesion of outer cortex of skull, 3 cm. in depth; clinical: "apple-size"	Radical removal of lesion of outer table	None 4 yr. later	Trauma to site at age 3, with "bump" developing 2 mo. later; mass grew for years
17	A 31530	Ossifying fibroma, mature	"Student" ?M	Mandible	.....	.....	.....	.....
18	A 55456	Ossifying fibroma, mature	76 N F	Hard palate	X-ray: protruding mass arising at junction of 2 maxillae, showing scattered bone formation and displaced teeth	Submucous resection, with extraction of teeth, of lesion attached to premaxilla	.....	3 cm. mass developed 2 yr. prior to removal, causing mechanical disturbances during eating
19	A 65004	Ossifying fibroma, mature	4 N M	Mandible	X-ray: mass involving ramus and body of mandible; clinical: 4 × 4 × 3 cm. mass at angle of L. mandible	Subtotal resection of L. mandible	None 4 mo. later	3 wk. of sudden growth in lump of 3 yr. duration; fistulized without draining
20	A 75222	Ossifying fibroma, mature	33 N F	Maxillary sinus	X-ray: mass of right maxilla; clinical: enlargement of R. maxilla	Complete removal of tumor	.....	Removal of upper molar 8 yr. prior to operation, followed in 1 yr. by asymptomatic swelling of R. frontal region
21	4308	Transition osteoma	49 W M	Frontal sinus	X-ray: clouding of frontal sinus and antra	External frontal operation	.....	Arthritis, sinusitis of antra, and nasal polyps
22	4949	Transition osteoma	29 N M	R. frontal sinus	X-ray: mass in frontal sinus	Incision at supraorbital ridge with removal of sinus wall and osteoma	None in 17 yr.	"Squint" and protrusion of R. eye 4 yr. prior to operation, with development of nodule
23	50128	Transition osteoma	15 W M	R. maxilla	X-ray: rarefaction of mandible near upper incisors	Local resection of lesion just bilateral to upper incisors	None	Growth of 4 mo. duration prior to operation
24	52384	Transition osteoma	26 W M	L. parietal bone	Clinical: soft vascular bone tumor with no invasion of dura or brain seen	Removal of tumor	None	Osteomyelitis developed at site of operation
25	60063	Transition osteoma	44 W F	R. parieto-frontal temporal region	X-ray: dense bone growth	Resection of tumor	None at 3 yr.	"Egg-shaped" mass since early age; some growth in previous 3 yr.

26	88787	Transition osteoma	32 W M	Frontal sinus	X-ray: filling of frontal sinuses, with extension through anterior wall	Resection of subperiosteal tumor, thinned frontal sinus wall, and osteoma in sinus	None	Injury to region 4 or 5 yr. prior to operation, with slow growth since
27	99078	Transition osteoma	15 N F	Maxilla	.....	.....	.....	.....
28	A 19031	Transition osteoma	16 N M	R. occipital region	X-ray: 9 × 9 cm. growth of outer table of skull	Resection of tumor, with bone graft	None at 3 yr.	Trauma to R. occipital region 3 yr. before operation
29	A 20014	Transition osteoma	44 N F	Fronto-orbital and nasal region	Clinical: orbital tumor destroying nose and causing blindness	Removal of tumor; postoperative sinus into ethmoids developed, removed; eye removed	.....	Obesity, arteriosclerotic heart disease
30	A 58037	Transition osteoma	42 N F	Mandible	.....	Resection of tumor	.....	Growth on lower mandible for 2 yr. prior to operation
31	5046	Osteoma, mature	25 W M	R. auditory canal	None	Removal of small mass in R. auditory canal	.....	An "auditory disturbance" once, probably unrelated to tumor
32	73636	Osteoma, mature	32 W F	R. frontal bone	X-ray: lesion not detected	Scalp incision with resection of 2 small bone masses	.....	Blow to R. frontal region at age 7; masses noted at age 12
33	79114	Osteoma, mature	8 W M	R. mandible	X-ray: no bone deformity of mandible	Removal of 2.5 cm. bone nodule from alveolar ridge of mandible	None at 9 yr.	Tooth knocked out from area; tumor developed 6 yr. prior to removal
34	98914	Osteoma, mature	42 W M	L. frontal bone	Clinical: large L. frontal mass	Removal of tumor, which extended to involve sphenoid and temporal bones; tantalum plate used	.....	Mass developed at age 4; several injuries to the site; headache, vertigo
35	A 18423	Osteoma, mature	73 W F	R. frontal bone	X-ray: area of increased density 2 × 3 cm. involving outer table	Periosteum elevated and a 1 cm. osteoma removed	None	Hypertension
36	A 25394	Osteoma, mature	11 N M	R. temporal fossa	.....	Intracranial removal of tumor	.....	Patient admitted with peritonsillar abscess and hemiplegia 7 yr. prior to operation; blindness of R. eye
37	A 43114	Osteoma, mature	10 N M	L. frontal bone	X-ray: area of increased density in L. frontal region behind sinus	Soft bony tumor involving inner table removed subperiosteally	None in 1 yr.	Tumor slowly enlarged for 2 yr. before operation
38	A 57719	Osteoma, mature	67 W F	Hard palate (torus)	Clinical: small mass on hard palate near teeth	Removal of mass	None at 2 yr.	Small mass appeared in tumor area 15 yr. prior to operation, following tooth extraction
39	A 60986	Osteoma, mature	55 N F	L. mandible	Clinical: 1 × 1 cm. mass over L. mandible	Submandibular approach, removal of tumor with osteotome	.....	Tumor noted 1 mo. prior to operation; some tenderness; hypertension
40	A 70899	Osteoma, mature	49 W M	L. mandible	Clinical: 1 cm. mass attached to alveolar ridge medially	Removal of mass	.....	Small growth noted 2 yr. before operation

lesion, however, is adherent to a thin outer bony sheet. Internal to this sheet is a solid mass of the same gritty, tan, fibrous, yielding but firm, sand-like, granular tissue which may be readily cut with a sharp knife and which submits with ease to frozen section. These gritty masses are found on microscopic examination to be trabeculae of bone, isolated islands, or separate nuggets of bone. The intervening stroma may be a dense, compact sheet of fibroblast-like cells which may contain areas of osteoid, or it may be loose fibrous tissue. In some areas a softer, yellow tissue may be present which proves to be more-typical fatty marrow. The inner margins are lobulated and distinct and give the impression of encapsulation, particularly to the surgeon. The inner limit may be a layer of eroded fibrous tissue or it may yet be covered by sinus epithelium. In the maturer forms of ossifying fibroma, coarser spicules or nuggets of hard bone are evident; there is more heterogenicity of the specimen, there being larger masses of softer fibrous tissue and sometimes masses of quite vascular inflammatory tissue. The picture may vary

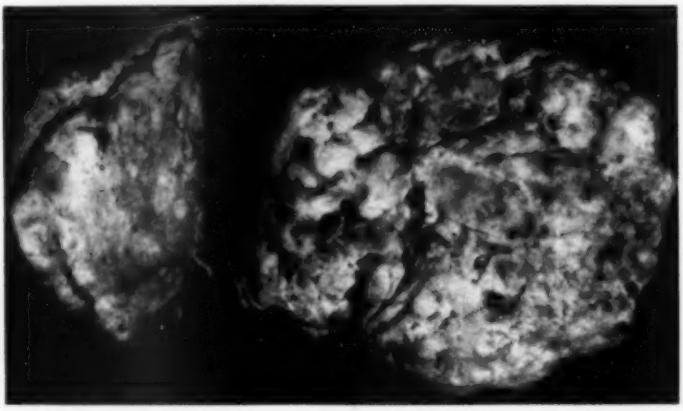


Fig. 2.—Gross specimen of a typical ossifying fibroma (Case 1, Table 1).

from area to area, particularly in the maturer forms, so that it is necessary to have a fair portion of the tumor for examination.

Explanation of Tables.—Table 1 summarizes the clinical data of our 40 cases. In an effort to define more clearly these lesions microscopically and to determine more cogently what relation, if any, ossifying fibroma bears to osteoma and to the sex and age of the patient, we have attempted to categorize the tumors in Table 2 on the basis of those histologic features which we believe can be commonly recognized, namely: solid cords of osteoblasts with or without interspersed osteoid, osteoid, giant cells separate from osteoclasts laying around bone, dense fibrous marrow stroma with wide fibrous cells, rounded islands of bone, layering of osteoblasts or osteoclasts around bone, trabeculae of bone, loose fibrous marrow stroma with narrow fibrous cells, inflammation, fatty marrow and hematopoiesis.

These features listed are arranged in what is thought to be a progressive order, with those mentioned first being more characteristic of young or fetal genesis of membranous bone and those mentioned last more characteristic of mature osteoma.

TABLE 2.—*Histologic Classification of Tumors*

Specimen No.; Patient's Age; Tumor*	Solid Cords of Osteoblasts	Osteoid	Giant Cells Separate from Osteoclast Layering Around Bone	Dense Fibrous Stroma and Wide Fibrous Cells	Islands of Bone	Layering of Osteoblasts or Osteoclasts Around Bone	Trabeculae of Bone	Loose Fibrous Stroma and Narrow Fibrous Cells	Other Osteoma Features
A 70504 (4; Y)	+	+	+	+++	++	+	+	....	.....
A 73080 (6; Y)	±	++	+	+++	++	+	....	....	.....
A 20561 (19; Y-I)	....	++	+	+++	+++	+	....	....	.....
A 58119 (15; Y-I)	....	+	+	+++	+++	+ in peripheral bone only	+	....	.....
76304 (24; I)	....	....	....	++	++	....	....	....	.....
94218 (27; I)	....	....	....	+++	++	+ in peripheral bone only	....	+	.....
A 17091 (17; I)	....	+	....	++	++	....	....	....	.....
A 31702 (29; I)	....	+	+	++	++	....	....	....	.....
A 33510 (10; I)	....	....	+	++	+	+	....	+	.....
A 38905 (16; I)	....	+	+	++	+	+	++	+	.....
A 46722 (26; I)	....	+	....	++	+++	+	....	+	.....
A 54260 (17; I)	....	±	....	++	+	....	....	....	.....
63510 (23; M)	....	+	....	++	+	....	+	+	.....
A 890 (43; M)	....	....	....	+	....	....	+	....	.....
A 20483 (5; M)	....	....	....	++	++	....	....	....	.....
A 29139 (11; M)	....	....	....	....	+	+	+	+	.....
A 31520 (Student; M)	....	....	....	++	+++	+	+	....	.....
A 55456 (76; M)	....	....	....	+	+	....	+	+	Inflammation ± Fatty marrow +
A 65004 (4; M)	....	+ in infected area	±	+ in infected area	+	....	+	+	.....
A 75222 (33; M)	....	....	+	++	++	+	+	....	.....
4208 (49; T)	....	....	....	....	+	+	++	++	Hematopoiesis ± Fatty marrow ±
4949 (29; T)	....	....	....	+	....	....	++	....	.....
50128 (15; T)	....	+	....	+	+	+	++	++	Inflammatory cells
52384 (26; T)	....	....	....	+	++	....	+	++	.....
60303 (44; T)	....	....	....	++	++	....	++	+	.....
83787 (32; T)	....	....	....	++	....	+ all clasts	+	+	Fatty marrow +
90078 (15; T)	....	....	....	+	+	±	++	++	.....
A 19031 (16; T)	....	....	....	+	....	....	++	+	.....
A 20014 (44; T)	....	....	....	....	+	....	+	+	.....
A 58937 (42; T)	....	....	....	....	....	....	++	++	Hematopoiesis + Fatty marrow ±
5946 (25; O)	....	....	....	....	....	....	++	++	Fatty marrow +
73630 (32; O)	....	....	....	....	....	....	++	++	Fatty marrow +
79114 (8; O)	....	....	....	....	....	....	++ (eburnation)	....	.....
98914 (42; O)	....	....	....	....	....	....	++	++	Fatty marrow +
A 18423 (73; O)	....	....	....	....	....	....	++	+	Fatty marrow +
A 25304 (11; O)	....	....	....	....	....	....	++	++	Hematopoiesis + Fatty marrow +
A 43114 (16; O)	....	....	....	....	....	....	++	++	Hematopoiesis + Fatty marrow +
A 57719 (67; O)	....	....	....	+	....	....	++	+	Hematopoiesis ± Fatty marrow +
A 60986 (55; O)	....	....	....	+	+	....	+	+	.....
A 70899 (49; O)	....	....	....	....	....	....	++	++	Hematopoiesis ± Fatty marrow +

* In parentheses, the number indicates the patient's age; "Y," a young ossifying fibroma; "Y-I," a young-to-intermediate ossifying fibroma; "I," an intermediate ossifying fibroma; "M," a mature ossifying fibroma; "T," a transition osteoma, and "O," a mature osteoma.

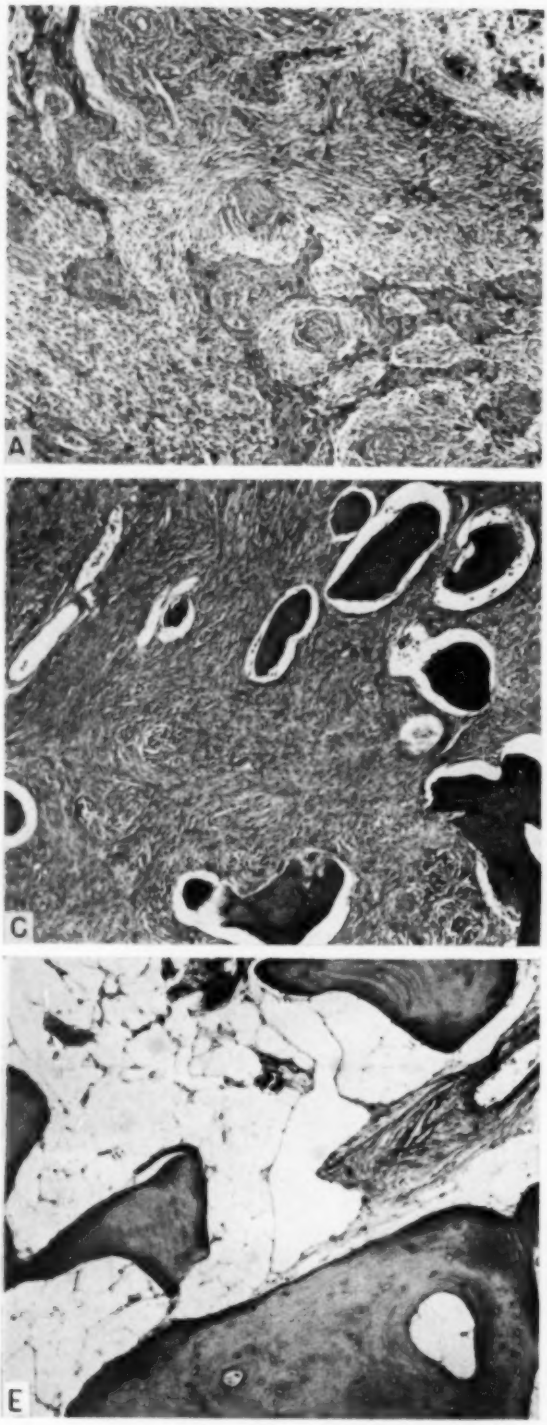
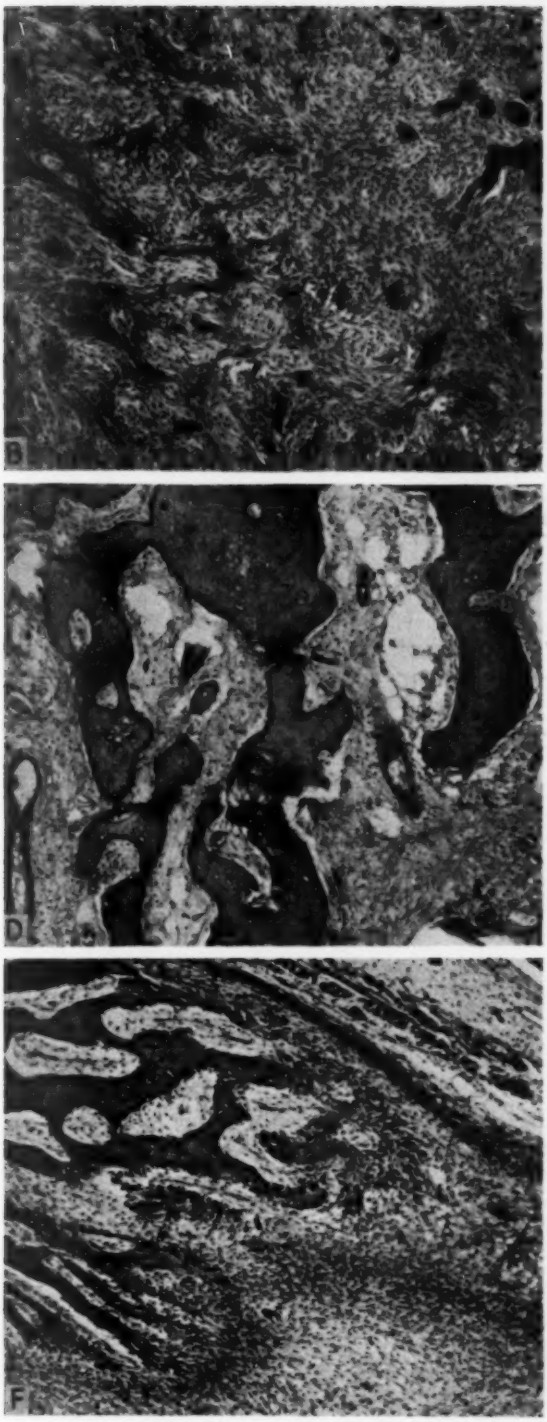


Fig. 3.—Photomicrographs showing (*A*) a young ossifying fibroma (Case 1, Table 1); (*B*) an intermediate (Case 30, Table 1); (*E*) a mature ostcoma (Case 40, Table 1), and (*F*) an intramembranous ossification of the



ossifying fibroma (Case 8, Table 1); (*C*) a mature ossifying fibroma (Case 20, Table 1); (*D*) a transition osteoma mandible of a fetus at 3 months. Compare with *A* and *B* for similarities.

The middle features may be seen in both ossifying processes and in some fibrotic variants of spongy osteoma. These variations with histogenetic sequence extend from the eburnated osteoma to the fibrous and giant-cell reactions with osteogenesis and finally to the formation of peculiar nonossified cords of osteoblasts or osteoblast-like cells. The osteoblast-cord appearance most closely resembles membranous ossification in the fetus (Fig. 3*F*), so that one is not surprised at such a close relation between this early normal process and the ossifying fibroma in the very young child. The osteoblastic cords may not be, however, and usually are not, solid cords of osteoblasts alone but have a very thin central core of osteoid or else are evenly dispersed through a stroma of osteoid, again being the true histologic counterpart of fetal membranous ossification. It is possible that some solid cords that are seen are due to sectioning in a plane nearly adjacent to and parallel with the osteoid core but not quite touching it.

In some instances groups of giant cells in dense fibrous stroma, such as those seen in giant-cell tumors, are found, but in our cases these were never in such great concentration as to lead one to consider a diagnosis of giant-cell tumor. The findings of dense fibrous stroma with wide fibrous cells apply to a dense sheet of fibroblasts or broad spindle-shaped cells similar to the picture seen in the fibrous tissue of a keloid, whereas the loose fibrous stroma and narrow fibrous cells apply to fibrocytes rather loosely arranged, such as one may find in the alveoli of the lung in resolving pneumonia or, even more sparsely, in normal fatty marrow. Islands of bone applies to those psammoma-like, apparently isolated, round masses of bone. Illustrations and an example of a case of this type in a female have been presented by Benjamins.[6] Any definitely elongated pattern, even though apparently isolated, is considered with the definite lattice-work struts of bone as trabeculae. Trichrome stains, such as the Masson and Mallory stains, prove of value in differentiating osteoid from true bone, as osteoid usually takes a connective-tissue stain, whereas bone ordinarily stains red. Other features were not considered significant enough to evaluate. Some of the ossifying fibromas contained considerable vascular tissue, such as that described as a constituent of fibrous dysplasia by Lichtenstein and Jaffe.[7]

The slides from each case were examined, and all the features listed were evaluated in four possible grades from zero to 3+. A diagnosis was then given to each case, according to which of the histologic features the growth possessed as follows: young, intermediate, or mature ossifying fibroma; transition osteoma, or mature osteoma. The young ossifying fibroma differs from the young-to-intermediate ossifying fibroma in exhibiting solid cords of osteoblasts and more prominence of the osteoblast-osteoid cords, with less collagenization of the stroma. The young-to-intermediate differs from the intermediate in the more striking presence of osteoid and giant cells separate from osteoclast layering around bone, the last two features not being constantly present in the intermediate ossifying fibroma. The intermediate differs from the mature ossifying fibroma in possessing more of

6. Benjamins, C. E.: Das Osteoid-Fibrom mit atypischer Verkalkung im Sinus frontalis, Acta oto-laryng. **26**:26, 1938.

7. Lichtenstein, L., and Jaffe, H. L.: Fibrous Dysplasia of Bone: Condition Affecting One, Several or Many Bones, Graver Cases of Which May Present Abnormal Pigmentation of Skin, Premature Sexual Development, Hyperthyroidism, or Still Other Extraskeletal Abnormalities, Arch. Path. **33**:777, 1942.

the younger features, such as osteoid, groups of giant cells, islands, or small newly formed trabeculae of bone with prominent peripheral osteoblast layers. Dense fibrous marrow stroma may be found in either type. The mature ossifying fibroma and the transitional osteoma are particularly hard to differentiate, the most important criterion being the relative amounts of dense fibrous tissue and loose fibrous tissue, the dense being more characteristic of the ossifying fibroma, together with smaller trabeculae or isolated trabeculae and prominent osteoblast layering. The transition osteoma is a spongy osteoma differing from the mature osteoma in possessing more of a dense fibrous stroma, as compared with normal fatty marrow present in the mature spongy osteoma. The osteoma eburneum is included in the mature group. Any one of the features listed was in no instance considered a pathognomonic feature of a given group, the relative amounts of the immature-to-mature features being evaluated in each instance; nor was there a single typical microscopic picture in each case but only an over-all impression.

The various cases were then tabulated in categories by their diagnoses to demonstrate more effectively the left-to-right transition.

TABLE 3.—*Summary of Data*

Pathologic Diagnosis	No. of Cases	Age Range, Yr.	Average Age, Yr.	Females/ Males	White Race/ Negro Race	Growth
Ossifying fibroma, young...	2	4-6	5	2/0	1/1	Appreciable in a few mo.
Ossifying fibroma, young to intermediate	2	15-19	17	2/0	0/2	Slow over many mo. or period of rapid growth
Ossifying fibroma, intermediate	8	16-29	21	5/3	4/4	Over 1 yr.
Ossifying fibroma, mature..	8	5-76	26	5/3	4/4	2 yr. or more
Transition osteoma	10	15-49	31	4/6	5/5	Usually over 2 yr.
Mature osteoma	10	8-73	37	4/6	7/3	Varied; tended to be over 2 yr.

The data are further analyzed in Table 3. Some growths may show areas of relatively greater or less maturity, but in such an event, the tumor was classified in the category of its less mature form. In no group was there a sufficient number of cases to be statistically significant.

ANALYSIS OF DATA

Some conclusions from the data listed in Table 3 are striking enough to be considered, despite the small number of cases falling in each group. The age progressively increases from that in cases of the young ossifying fibroma to that in cases of the osteomas. The female sex preponderance in the entire ossifying-fibroma group is another interesting feature, although it will be noted that the ratio is reversed in the osteoma group. Also, the age spread (8 to 73) in the mature-osteoma group and the occurrence of mature osteomas in persons under 12 years of age seems to indicate that this process has enough individual distinction to begin as osteoma and to remain osteoma throughout its existence in some instances. In this connection it should be noted that all four of the osteomas occurring in persons under the age of 26 were in males, with three occurring before the age of 12. Our data and data from the literature are further considered and evaluated by topic hereafter.

Age.—The tendency for ossifying fibromas to occur in younger age groups than osteomas was probably a factor influencing Geschickter and Copeland,[3] who stated that ossifying fibromas actually evolve in time to spongy osteomas and "thence to eburnated osteomas." Their series of 30 ossifying fibromas and 40 osteomas revealed an average age for each entire group of 14 years for the ossifying fibromas and 40 years for the osteomas. Our entire series reveals an average age of 21 for the ossifying fibromas and 34 for the osteomas. To exclude osteomas in persons under 12 years of age gives an average age of 48. This fact points to two peaks in the osteoma groups—one in the very young with a mean at about 10 years and one in adults with the mean at 48 years. The young group in our meager series shows a marked preponderance of males, all three patients being male, while in the older groups, there is an even distribution of 4 females to 3 males.

The average age of 14 patients reported on by Schlumberger [1] as having fibrous dysplasia of the cranial bones, maxilla, and mandible was 24.6 years, but this series is mostly of young men of military age, and the age figures are, therefore, of restricted comparison value.

Teed [8] found in an analysis of 250 osteomas that the largest group occurred in the third decade. The average age in his series was 35.7 years. However, here again there was no attempt to define pathologically or differentiate ossifying fibroma from osteoma. A. T. Smith [9] stated that osteomas were featured by occurrence in younger age groups, but ossifying fibromas were apparently included as osteomas.

Sex.—There is a distinct sex preponderance for the occurrence of the entire ossifying fibroma group in the female (Table 3). This is especially true of the four young ossifying fibromas, which compose a group in sharp contrast to the three mature osteomas in young persons, all of which occurred in males. Again it should be emphasized that in this small a series these figures can at most only point out a trend for further studies.

Comparisons with other studies of the sex incidence is difficult. Geschickter and Copeland [3] did not analyze their cases as to sex, and we know of no other series of comparable size. Schlumberger's [1] series of 14 cases of fibrous dysplasia (ossifying fibroma) were all in white males, an observation reflecting the predominance of males in the armed forces.

In a series of 51 "osteomas" reported by Hallberg and Begley,[10] 36 were in males and 15 in females. These authors did not list the microscopic descriptions, so it is not possible to separate the various classes of histologic variants. In Phemister and Grimson's [4] series of ossifying fibromas of the jaw, in 14 cases of which the sex was reported, 9 were in females and 5 in males, an observation again demonstrating the predominance of this lesion in females.

It is perhaps worth noting that a late menarche was occasionally recorded in our series (Table 1), while pubertas praecox is a feature among cases of polyostotic fibrous dysplasia.

8. Teed, R. W.: Primary Osteoma of the Frontal Sinus, Arch. Otolaryng. **33**:255, 1941.

9. Smith, A. T.: Osseous Lesions of the Nose and Sinuses with Special Reference to Hypertrophic Changes and Tumor Formations, Arch. Otolaryng. **31**:289, 1940.

10. Hallberg, O. E., and Begley, J. W.: Origin and Treatment of Osteomas of the Paranasal Sinuses, Arch. Otolaryng. **51**:750, 1950.

We have no explanation for the preponderance of fibrosing lesions in females and of mature osteomas in males. In this connection, it is interesting that in a study of the various types of fibromatoses, a peculiar relation of the disease in females and even female predominance in some series was noted.[11] Explanations available for pensive conjecture include those postulating a reaction to, or concentration of, gonadotropic and estrogenic hormones in the tissues of these various fibromatoses and fibrous tumors.[12]

Race and Heredity.—As will be seen from Table 3, no predominant tendency of either ossifying fibroma or osteoma to occur in either the white or the Negro race is observable. Most of the patients in this series resided in North Carolina, where the high percentage of Negroes in the population would explain the almost even distribution between the white and Negro races noted. No evaluation of race incidence was made by Geschickter and Copeland. Handousa [12a] reported 18 cases in Egyptians. It would seem probable that there is no race predilection among these lesions.

We found no familial trait in our cases.

Recurrence.—In our series of 40 cases, there were only 2 with documented recurrence. In Case 9 the lesion recurred and was resected four years after the first operation. The histologic sections of the recurrent lesion showed little variation from the original lesion. In Case 15 the lesion recurred and was resected three years after the first operation and recurred again two years after the second operation. A third operation was not done, as the parents of the child felt that the lesion was not greatly disfiguring. The slides of tissue from the second operation showed some slight increase in fat and capillaries in the tissue between bone trabeculae.

Trauma.—The role of trauma is commonly mentioned as a significant factor in the literature on osteomas. A. T. Smith [9] said that some osteomas may begin after trauma. In our cases, a history of previous trauma to the area involved by the tumor was obtained in four cases of ossifying fibromas, all classified as mature, and in five cases of osteomas. In the few instances in which blood calcium and phosphorus levels were determined, they were found to be normal.

Clinical Course.—The clinical course of ossifying fibromas and osteomas is variable. As Table 1 shows, the tumor may grow rapidly at first, reaching objectionable size within a year's time, but may then become stationary, or it may increase in size very slowly. Some may be discovered only as incidental x-ray findings. As a rule, the periods of more rapid growth occur at a younger age, but this is not always true. Some tumors may reach large size and sequestrate of their own accord.[13] If incompletely removed, ossifying fibroma will recur and may grow to the size of the original tumor, as, for example, in our Cases 9 and 15 (Table 1).

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11. Pickren, J. W.; Smith, A. G.; Stevenson, T. W., and Stout, A. P.: Fibromatosis of the Plantar Fascia, Cancer **4**:846, 1951.

12. Geschickter, C. F., and Lewis, D.: Tumors of Connective Tissue, Am. J. Cancer **25**:630, 1935. Lipschultz, A., and Grismali, J.: On the Anti-Fibromatogenic Activity of Synthetic Progesterone in Experiments with the 17-Caprylic and Dipropionic Esters of α-Estradiol, Cancer Res. **4**:186, 1944.

12a. Handousa, A. S.: Osteomata, J. Laryng. & Otol. **55**:197, 1940.

13. Paget, J.: Lectures on Surgical Pathology: Hypertrophy, Atrophy, Repair, Inflammation, Mortification, Specific Disease, and Tumors, Philadelphia, Lindsay & Blakiston, 1854, p. 463.

Evaluation of the duration of the lesions is rather difficult, particularly with regard to osteomas, which may be present for considerable time, never giving rise to symptoms. It is almost certain that even in ossifying fibromas there is a certain latent period prior to the clinical symptoms. Geschickter and Copeland [3] indicated that for ossifying fibromas in their series the duration of symptoms was 45 months, whereas for osteomas it was 14 months. These figures can be subjected to many qualifications but perhaps indicate that once an osteoma does produce symptoms the symptoms quickly become aggravated. This fact may be due to the tendency of some osteomas of the sinuses to produce a severe concomitant sinusitis. In our series, in general the patients in the ossifying-fibroma group had symptoms from one to four years and those in the osteoma group from one to six years or more prior to surgical intervention, although there was considerable variation among individual patients. Both lesions are usually painless unless complicated by infection.

Change of osteoma into osteogenic sarcoma has been reported.[10] Other complications include obstruction of the nasofrontal duct with pyocele or mucocele, exophthalmos, enophthalmos or destruction of the eye, mental disorder (from extension into the cranial cavity), epilepsy, vertigo, cerebrospinal rhinorrhea, meningitis,[8] and pneumocephalus.[14]

Some cases of conservative therapy or of x-ray therapy illustrate the fact that after the initial-growth phase, the lesion may remain static, causing no further trouble.[15] More radical therapies include many bizarre procedures. Some osteomas were formerly attacked by piecemeal chiseling at the mass, with the frequent result of erysipelas.[12] There is a case of self-treatment with a strong acid with final successful eradication, the tumor eventually falling out.[8] For further discussion of the clinical features and operative treatment of osteomas, the reader is referred to more extensive accounts devoted entirely to these features.[16]

In our series no lesions were noted in bones other than cranial or facial bones. Although extensive skeletal surveys were not usually done, the cases were followed long enough so that if other lesions or a more extensive fibrous dysplasia had been present, clinical evidences of these would have appeared.

Histologic Criteria.—It is impossible for us to tabulate properly and analyze comparative data from the literature as to histologic criteria and their relation to sex, age, or other clinical characteristics because of the lack of photomicrographs in most of the previously reported cases of fibrous or bony lesions of the face or cranium. No true division between osteomas and fibrous dysplasia has generally been made. Some lesions were typical examples, histologically, of intermediate and mature fibrous dysplasia (ossifying fibromas) in young females and were called osteomas (Priest and Boies,[15] Rawlins [Case 2],[17] Fetissof,[18] and A. T. Smith [9]).

14. Brunner, H., and Spiesman, I. G.: Osteoma of the Frontal and Ethmoid Sinuses, Ann. Otol. Rhin. & Laryng. **57**:714, 1948.

15. Priest, R. E., and Boies, L. R.: Osteoma of the Maxillary Sinus, Ann. Otol. Rhin. & Laryng. **51**:79, 1942.

16. Teed.[8] Hallberg and Begley.[10]

17. Rawlins, A. G.: Osteoma of the Maxillary Sinus, Ann. Otol. Rhin. & Laryng. **47**:735, 1938.

18. Fetissof, A.: Pathogenesis of Osteomas of the Nasal Accessory Sinuses, Ann. Otol. Rhin. & Laryng. **38**:404, 1929.

Suffice it to say that in those cases that are accompanied by photomicrographs, we believe that we can detect the same sex and age tendencies for young and intermediate ossifying fibromas, as opposed to osteoma eburneum and mature osteoma, as noted in our own cases.

THE NATURE OF THE DISEASE

The nature and pathogenesis of facial and cranial bone lesions are not readily crystallized concepts. Interesting early accounts and debates on their nature may be sifted from Sir James Paget's material. He cited a case in a 15-year-old girl "in whom enlargement of the nasal process of the superior maxillary bone had been observed for eight years and was still increasing." [18] The lesion was described as an "osseous tumor." A similar facial deformity in a 22-year-old woman was described as a "myeloid tumor" (giant-cell tumor) of the maxilla. It is possible that the inclusion of a mixed group of lesions in the "myeloid" group contributed to the objections of Virchow, who felt that Paget's "myeloid" tumors were in reality sarcoma.[19]

Pathogenesis.—There is a theory of pathogenesis that those osteomas that occur in the frontal sinus arise from the junction point of the ethmoid with the frontal bone. The ethmoid preforms in cartilage, and there is a cartilaginous nubbin at this junction that presumably gives rise to osteomas, somewhat after Cohnheim's congenital-rest theory of neoplasia. Proponents of this theory according to Fetissof [18] were Arnold, Boenninghaus, and Rokitansky, who believed that all exostoses were ossified chondromas. However, Teed [8] said that only 26 of 128 cases in the literature could have arisen from this junction site, and Hallberg and Begley [10] stated that only 4 of their 40 cases of osteoma of the frontal sinus originated there. Infection has been implicated.[20] We have found instances of an apparent new nidus of ossification occurring in an area of inflammation, which suggest that under certain circumstances infection may play a role (our Case 21). Other ideas listed by Fetissof are the belief of Cloquet that osteoma was an ossified polypus, Virchow's theory of development from diploe of bone,[18] and origin from an intradiploe "corps osseux enkyste," as suggested by Cruveilhier. Teed [8] cited Dolbeau as proposing the origin as by ossification of the mucoperiosteum of the sinuses. There are adherents to the idea of development from the periosteum and its variations, such as ossification of a fibrous matrix in communication with or arising from the periosteum.[18] Echlin [21] studied cranial osteomas and decided that "certain osteomas arise from preosseous tissue on the cranial surface and that these osteomas when actively growing are spongy and usually absorb the outer table of the skull, but when slowly growing or when the end stages of ossification have been reached, they are eburnated and usually relatively quiescent" and that they may be regarded as arising in the deeper layers of the periosteum or else subperiosteally, according to one's definition of

19. Virchow, R.: Die krankhaften Geschwülste; Dreissig Vorlesungen, gehalten während des Wintersemesters 1862-1863 an der Universität zu Berlin, Berlin, August Hirschwald, 1864-1867, Vol. 2, p. 5.

20. Ersner, M. S., and Saltzman, M.: Osteoma of the Sinuses, Laryngoscope **48**:29, 1938.

21. Echlin, F.: Cranial Osteomas and Hyperostoses Produced by Meningeal Fibroblastomas: Clinical Pathologic Study, Arch. Surg. **28**:357, 1934.

the word periosteum. Echlin reported some cranial osteomas arising from the inner table of the skull or endocranium but believed he had seen no example arising from the diploe. He studied similar lesions of the jaws and concluded:

These benign ossifying lesions, like the cranial osteomas, arise subperiosteally and are characterized in the roentgenogram by a spongy transformation of membranous bone, extending outward from which is a smoothly outlined dome. On the surface of this dome is sometimes present a shell of newly formed bone. This bony shell has often been mistaken for the expanded cortex of the underlying bone.

With regard to the pathogenesis of fibrous dysplasia, Jaffe [21] stated:

We know nothing of the etiology of the condition, but the systemic character of the disease complex as a whole strongly suggests that it has its basis in some deep rooted developmental defect, though it does not show any familial or hereditary factor. In a sense, the individual bone lesion may be conceived of as a hamartoma—that is, a tumor-like malformation resulting from flaws of development and characterized by defects of tissue combination.

Developmental Aspects.—The cranial and facial bones are for the most part membranous bones as compared with bones preformed in cartilage in most of the remainder of the skeleton. The implications of this fact are far-reaching in any argument as to etiology, in proper terminology, and in the attempt to separate definitely skeletal exostoses from cranial or facial osteomas or to define osteomas as bone tumors restricted to the cranium and face. The bones specifically that form by intramembranous ossification are the parietal and frontal bones; the squamous and tympanic portions of the temporal bone; the median pterygoid plate of the sphenoid bone; the nasal, lacrimal, malar, and palatine bones; the vomer; the maxilla, and most of the mandible.[22]

The ages given in Table 3, particularly for the four youngest ossifying fibromas, and those for the three youngest osteomas lead one to suspect strong developmental connections or some unexplained interference with the normal intramembranous ossification processes, because of the striking lesions in children, regardless of whether one accepts a predominantly tumorous origin or a predominantly developmental origin.

The disease is not a new one phylogenetically. Frontal-sinus osteomas have been reported in elk, oxen, sheep, and goats,[23] a fact indicating no specific etiologic or growth factor in man alone.

Relation to Other Lesions and Definition of Terms.—The primary process in the production of osteoma is ossification, and one may perhaps rightly refer to any abnormal mass of osseous tissue as osteoma. However, Ewing [24] divided osteomas into primary or secondary, the primary being growths more characteristically of autonomous and expansive character occurring in facial bones, and the secondary being such osseous transformations as occur in fibroma, lipoma, sarcoma, nervous system osteoma, heteroplastic bone formation, osteoid osteoma, and myositis ossificans. Ewing specifically mentioned "true" osteomas of facial bones as occurring in very young females, even congenitally. We wonder whether indeed these were not

22. Morris, H.: Morris' Human Anatomy: A Complete Systematic Treatise, edited by J. P. Schaefer, Ed. 10, Philadelphia, The Blakiston Company, 1942. Echlin.[21]

23. Gatewood, W. L., and Settel, N.: Osteoma of the Frontal Sinus: Review of Literature and Report of a Case Presenting Extended Invasion of Orbit, Arch. Otolaryng. **22**:154, 1935.

24. Ewing, J.: Neoplastic Diseases: A Treatise on Tumors, Ed. 4, Philadelphia, W. B. Saunders Company, 1940.

the same as our ossifying fibromas in four young females, a fact which would indicate Ewing's feeling that these lesions are in reality osteomas. This fact is of particular interest in view of the present tendency to group these lesions as fibrous dysplasia. The completely ossified osteochondroma or exostosis is included by some. Virchow included these lesions as well as hyperostoses and other exostoses under the heading "osteoma." Geschickter and Copeland regarded osteoma as peculiar to membranous bone. Lichtenstein [24a] said that the term osteoma is a much-abused one. He restricted its use to "certain bony growths of appreciable size, which arise particularly in bones of the skull preformed in membrane, and are rather prone to extend into the orbit or into one or another of the paranasal sinuses." There are, then, the all-inclusive and the specific uses of the term; the all-inclusive one including any growth with a histologic appearance of bone occurring in an unusual site or representative of unusual osseous growth, and the specific use being confined to osteomas of the facial or cranial bones.

The relation to simple fibroma of bone called "nonosteogenic fibroma of bone" by Jaffe and Lichtenstein [25] naturally arises. In general this fibroma is distinguished by its lack of ossification and greater circumscription, and need not really be confused except for some new ossification which may occur at the periphery of the lesion. Jaffe [2] pointed out the possible confusion of fibrous dysplasia, particularly polyostotic, with multiple enchondromatosis. This confusion has particular reference to the x-ray diagnosis. Other links of fibrous dysplasia to specific entities have been raised, such as the belief that it is a form of neurofibromatosis or Hand-Schüller-Christian disease, and these have been dealt with by Jaffe.[26] The differentiation from osteitis fibrosa cystica, or Recklinghausen's disease of bone, was made by Lichtenstein [27] and Jaffe [7] in their earlier papers. They also indicated the identity of Albright's "osteitis fibrosa disseminata" with polyostotic fibrous dysplasia.

Other terms which should be considered in this connection include those synonymous with ossifying fibroma, such as osteofibroma and fibro-osteoma. These do not actually represent separate diseases. Our ossifying fibroma is not "osteitis fibrosa" as the term was used by Geschickter for variants of bone cyst. Fibrosis of marrow secondary to trauma, fracture, or infection we prefer to call "myelofibrosis." Lichtenstein [24a] defined an "osteogenic or ossifying fibroma of bone" composed of "highly vascular connective tissue tumors exhibiting active osseous metaplasia." There are osteoid, new bone, large spindle cells, and giant cells in this lesion, which is characterized by a benign clinical course and occurrence in the vertebrae, flat bones, and bones of the hands and feet. This lesion, Lichtenstein stated, may be "bracketed under the head of the 'spindle-cell variant of the giant-cell tumor' by Geschickter and Copeland." We have seen examples of what seem histologically to be similar processes in the bony growths which occur off the alveolar ridges of the mandible or maxilla, yet these do not, by virtue of their

24a. Lichtenstein, L.: Bone Tumors, St. Louis, C. V. Mosby Company, 1952.

25. Jaffe, H. L., and Lichtenstein, L.: Non-Osteogenic Fibroma of Bone, Am. J. Path. **18**:205, 1942. Hatcher, C. H.: The Pathogenesis of Localized Fibrous Lesions in the Metaphyses of Long Bones, Ann. Surg. **122**:1016, 1945.

26. Jaffe, H. L.: Fibrous Dysplasia of Bone: Disease Entity and Specifically Not an Expression of Neurofibromatosis, J. Mt. Sinai Hosp. **12**:364, 1945.

27. Lichtenstein, L.: Polyototic Fibrous Dysplasia, Arch. Surg. **36**:874, 1938.

28. Footnote deleted.

location, entirely fit into this ossifying group of Lichtenstein or, by virtue of their ossification, fit classic forms of epulis.[29] They are more cellular and variegated than the usual picture Lichtenstein and Jaffe described for fibrous dysplasia. This fact is mentioned to indicate that we include lesions of the fibrous-dysplasia histologic type and those bearing some histologic relation to Lichtenstein's ossifying fibroma in our ossifying-fibroma group, such complexities indicating to us the difficulty and impropriety of histologic distinctions among these various multinamed lesions; they should all be considered in relation to a study of osteoma of the facial and cranial bone areas, regardless of which term one individually prefers. Monostotic fibrous dysplasia of cranial or facial bones is interpreted by us as synonymous with what we are calling ossifying fibroma, just as ossifying fibroma is interpreted by Schlumberger [1] as fibrous dysplasia.

ARGUMENT

Bone is almost unique in the adult body in retaining its powers of development from a fibrous-like tissue, or multipotent mesenchyme, to undergo growth changes, as in fractures, perfectly reduplicating its fetal ontogenetic relations. Nor must this mesenchyme always be that intimately associated with the formed or adult bones, the nidus for bone formation being universally pervasive in the body in the form of fibroblasts, which, in the concept of Ewing, undergo metaplasia, "the fibroblasts acquiring the function of osteoblasts." [24] This results in those fascinating examples of heterotopic bone formation—in the walls of arteries, in the tendon sheaths, in the muscles as myositis ossificans, in some long-standing calcific deposits, in the organization of dead tissue or blood clot, or in the parenchymal organs. Bone histologically has several variants in reaction to stimuli of all types, and all types of stimuli will result in only these commonly seen variants. Yet the combination of these histologic variants may be in just such a manner, giving dominance to one cell type, as to suggest some peculiar and as yet poorly understood process. There are examples of mystifying variants of nonmetastasizing bone conditions, not all adequately explained, as in the case of Jaffe and Mayer [30] and of Blumberg, Dehne, and Forbus.[31]

This complexity of fibrous processes in bone complicates the thorough study of lesions of the type considered in this article. It is to be hoped that repeated siege may eventually satisfactorily separate the various entities, but such siege is upon a groundwork of metabolic research and can perhaps be resolved only with a greater knowledge of the nature and causation of tumors.

The separation of osteoma of the cranial and facial bones from ossifying fibroma is attended with these difficulties, and yet thoughts on the subject are desirable. Sharp separation of the two enables one to conceive a unity of facial and cranial ossifying fibroma and polyostotic and monostotic fibrous dysplasia, whereas inability

29. Thoma, K. H.: Oral Pathology: A Histological, Roentgenological, and Clinical Study of the Diseases of the Teeth, Jaws, and Mouth, Ed. 2, St. Louis, C. V. Mosby Company, 1944.

30. Jaffe, H. L., and Mayer, L.: An Osteoblastic Osteoid Tissue-Forming Tumor of a Metacarpal Bone, Arch. Surg. **24**:550, 1932.

31. Blumberg, J. M.; Dehne, E., and Forbus, W. D.: Spontaneous Activation and Progressive Differentiation of Mesenchymal Foci in the Bones, Simulating Destructive Neoplasia, but Terminating in Fibrosis, Calcification, Ossification, and Complete Cessation of Proliferative Activity, Bull. Hosp. Joint Dis. **12**:443, 1951.

to do so implies unity of osteoma and ossifying fibroma, thus meriting a categorization of the facial or cranial ossifying fibroma separate from monostotic or polyostotic fibrous dysplasia.

We think that the gradual increase in age with evidence of advancing histologic maturity, particularly when the analysis is confined to females, is a strong factor in support of Geschickter and Copeland's view of the evolvement of ossifying fibroma into osteoma. This feature led us to suspect such a connection even before we learned of Geschickter and Copeland's conclusions. The crucial evidence in this matter must, however, come from repeated biopsies of a facial or cranial bone lesion, without removal of the lesion, over a period of 10 to 20 years. We have no such example among our cases.

The differentiation between spongy osteomas with dense fibrous marrow and some ossifying fibromas is a pathologist's nicety, subject to all the arbitrary rules and debate of many different individual concepts. It is this undefinable limit and close association that might lead one to believe that osteoma and ossifying fibroma cannot be definitely separated histologically and are very closely related and that some ossifying fibromas may eventually become typical osteomas. The x-ray films, gross appearance, and clinical course may equally fail to enable one to make a sharp distinction.

It cannot be denied that certain forms of facial or cranial bone disease appear to be entirely components of polyostotic fibrous dysplasia. These include some with generalized involvement of bones of the skull,[32] leontiasis ossea, and any examples of multiple bone involvement or of single facial bone involvement with involvement of other bones of the body. Instances of multiple cranial bone involvement with involvement of other skeletal bones are cited by Lichtenstein and Jaffe.[7]

The nature of changes in the histologic picture in ossifying lesions and osteomas is important. Lichtenstein and Jaffe recognized progressive histologic changes in both osteoma and ossifying fibroma. Lichtenstein [28] stated in reference to osteoma: "Cytologically, these growths are composed essentially of osteoblastic connective tissue, forming abundant osteoid and new bone, which may eventually become rather compact." He recognized, then, a certain degree of progressive cytologic change only in the osteoma group. Jaffe [2] defined a tendency toward stabilization in fibrous dysplasia, saying: "Active progression of the skeletal involvement tends to end when adult life is reached . . . . Thus, even when fibrous dysplasia of bone is first uncovered in adult life, the skeletal lesions apparently date back to childhood." He described an "increasing ossification of the fibro-dysplastic tissue as another aspect of the process of stabilization" and said, "In fact, in some cases (particularly in the skull though also in some long bones) sclerotization of the fibro-dysplastic tissue may become very pronounced." He did not, however, refer to this sclerotization as the genesis of an osteoma. He believed this tendency to stabilization does not prevent a tremendous increase in size of the lesion even during adult life, and certainly this postulate is necessary to interpretation in the present study, as there are undeniable instances [1] (Table 1) of such increase in size in "sclerotic" lesions of the facial bones of adults. Nevertheless, Jaffe did find that skull lesions, particu-

32. Billing, L., and Ringertz, N.: Fibro-Osteoma: Pathologico-Anatomical and Roentgenological Study, Acta radiol. **27**:129, 1946.

larly, showed a tendency to sclerotization, a fact which in our minds serves to separate these from the main body of fibrous dysplasia. The progression of ossifying fibroma or fibrous dysplastic processes into osteoma is not, however, a hard and fast rule, as previously indicated, for we believe that some osteomas, particularly those in young males, originate in the histologic transition or mature osteoma form and remain so throughout their existence. Certainly, also, some ossifying fibromas are surgically removed while still in their young or intermediate stages and hence cannot be observed subsequently. The occurrence of the mature ossifying fibroma in women as old as 43, 53, and 76 suggests that in some instances the cycle is never completed. It must be allowed that, until such progression is conclusively demonstrated by repeated biopsy over a period of years, it remains only a belief and that the two groups, ossifying fibroma and osteoma, may, in truth, be separate entities.

Another argument against academic categorization of osteoma with facial or cranial ossifying fibroma is that, even though sclerotization does occur, the lesion was not originally altogether of an osteoblastic or osseous-tumor nature but included nonspecific fibrous tissue and hence the final result is not osteoma but sclerotized fibrous dysplasia. We believe an attempt to distinguish between osteoblasts derived from osteoblasts and osteoblasts derived from fibrous-like cells, and an attempt to place the diagnosis of osteoma on such a basis, are at once complex and without strongly persuasive factual support.

It is only natural to reason that since the normal end-result of fetal membranous ossification is mature bone, the expected result of a mass of similar fibrous ossifying tissue is an osteoma—without previous formation in cartilage it is not an osteochondroma, and yet it arises from bone and hence is not a secondary osteoma or heterotopic bone.

A histologic feature of distinction between the facial lesions and those occurring elsewhere in the body is the absence of cartilage. Lichtenstein and Jaffe [7] described hyaline cartilage as an integral part of the dysplastic process. We found none in in our cases.

Regardless of the underlying pathologic concept, these facial and cranial lesions, irrespective of their histologic picture, forcibly impress clinicians with their tumorous nature by virtue of their apparent spontaneous origin as autonomous growths, usually unassociated with other disease, and it is this common clinical appearance that has resulted in the consideration of lesions of the ossifying-fibroma and fibrous-dysplasia group by clinical authorities as osteoma.

In further support of the separation of membranous-bone ossifying fibroma from the main body of fibrous dysplasia and its alliance with osteoma, we cite the views of Davies-Colley [33] and the previously mentioned series of Geschickter and Copeland.[8]

The pathogenic mechanisms of ossifying fibroma and polyostotic fibrous dysplasia could easily be identical, but then so could the primary mechanisms in the production of all tumors be identical and be at least closely related to the origin of fibrous dysplastic processes.

33. Davies-Colley, R., in discussion on Fibrocystic Disease of Bone, Proc. Roy. Soc. Med. **27**:973, 1934.

The argument cannot but remain unsettled. The clinical appearance, the solitary nature, the tendency to sclerotization, the absence of cartilage, and the progressive change in the histologic variants with age with the absence of a sharp histologic line of distinction between mature ossifying fibroma and transitional osteoma in our minds serve to separate ossifying fibroma from fibrous dysplasia for the purpose of clinical convenience and for classification. The same factors also ally ossifying fibroma and osteoma of facial and cranial bones as related processes to be considered together, irrespective of the actual terms used and irrespective of whether one prefers to think of ossifying fibroma as monostotic fibrous dysplasia, although it would seem that some osteomas possess a single histologic appearance throughout their existence and do not arise from a preexisting ossifying fibroma.

SUMMARY

A series of 20 ossifying fibromas and 20 osteomas of cranial and facial bones is presented and analyzed, and their terminology is discussed.

Arguments are given in support of the consideration of osteoma and ossifying fibroma (monostotic fibrous dysplasia) of cranial and facial bones in the same clinical and pathogenic group, as opposed to their complete separation and as opposed to the identification of ossifying fibroma as only a form of fibrous dysplasia.

HYALINE MATERIAL WITH STAINING REACTION OF FIBRINOID IN RENAL LESIONS IN DIABETES MELLITUS

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FOLLOWING independent communications by Kimmelstiel and Wilson [1] and Murakami,[2] several reports have appeared describing in great detail a peculiar nodular lesion found in glomeruli of kidneys of diabetic patients. An excellent summary of the literature pertaining to this lesion and to associated clinical manifestations can be found in a recent review by Kimmelstiel and Porter.[3] Bell [4] considered diffuse sclerosis of the loops of the glomerular tuft as another significant renal lesion associated with diabetes mellitus.

Study of a large series of kidneys of diabetics afforded the opportunity to investigate advanced renal lesions associated with this disease. It soon became clear that the glomerular changes are not confined to nodular lesions and to lesions of diffuse sclerosis of glomerular capillaries but that other morphological alterations can be observed as well.

It is the purpose of this paper to focus attention primarily on a glomerular lesion found predominantly in kidneys of diabetics with severe renal damage. The lesion is characterized by deposits of hyaline material displaying the staining reaction but not the morphological appearance of fibrin. Since the material has all the staining characteristics of fibrinoid, as mostly compiled recently by Altshuler and Angevine,[5] it was decided to designate it by the descriptive term "hyaline-fibrinoid." [6]

The hyaline-fibrinoid material differs structurally and tinctorially from the aforementioned glomerular lesions associated with diabetes. The added significance of this observation is seen in the fact that deposits of similar material may be found

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1. Kimmelstiel, P., and Wilson, C.: Intercapillary Lesions in the Glomeruli of the Kidneys, Am. J. Path. **12**:83-98, 1936.

2. Murakami, R.: Beitrag zur Kenntnis der Veränderung des Nierenkörperchens beim Diabetes mellitus, Tr. Soc. path. jap. **26**:657-664, 1936.

3. Kimmelstiel, P., and Porter, W. B.: Medical Progress: Intercapillary Glomerulosclerosis, New England J. Med. **238**:876-879, 1948.

4. Bell, E. T.: Renal Diseases, Ed. 2, Philadelphia, Lea & Febiger, 1950.

5. Altshuler, C. H., and Angevine, D. M.: Histochemical Studies on the Pathogenesis of Fibrinoid, Am. J. Path. **25**:1061-1077, 1949.

6. It should be emphasized that the term "fibrinoid" is used in a strictly descriptive sense and refers to certain staining characteristics of the material and not to the underlying basic alterations of tissue. It is entirely beyond the scope of the present paper to discuss the nature of the "fibrinoid" change.

in the parietal layer of Bowman's capsule and the basement membrane of the proximal convoluted tubules. Furthermore, staining properties of certain diseased arterioles, displaying the hyaline type of arteriolar sclerosis, as well as of tubular casts of inspissated protein, are identical with those of the hyaline-fibrinoid material.

In 1936 Kimmelstiel and Wilson,[7] using the term "alterative glomerulitis," described areas of hyaline glomerular necrosis which had the staining properties of fibrinoid. They linked this change with hypertension but not with diabetes. The lesion they observed, as illustrated by their Photographs 2, 3, and 4, corresponds very closely to the hyaline-fibrinoid glomerular lesion with which we are concerned here.

Further perusal of the literature revealed that Fahr [8] was apparently the first to notice this distinct glomerular lesion in diabetic kidneys. Subsequently, Spühler and Zollinger [9] described the lesion with considerable detail, using the term glomerular fibrinoid caps. These communications were followed by a paper by Wernly,[10] who in a series of ingenious diagrams illustrated in an interesting fashion the relationship of the nodular lesions and hyaline glomerular caps and considered the two as being distinctly different. In a more recent communication, Hall [11] briefly described what he termed the exudative lesion of diabetic glomeruli.

It was not until May, 1952, while this paper was in preparation, that the first American communication on this subject appeared. Barrie, Aszkanazy, and Smith [12] described the presence of "fibrin caps" in glomeruli of diabetics. The morphological observations of these authors accord to a large extent with my own. A possible indication that the lesions which I have undertaken to describe may have been noticed previously in diabetic kidneys is found in a paper by Simon,[13] who mentioned without elaboration lipohyaline material present in the glomeruli. Allen [14] noticed hyaline-fibrinoid material in the tubular basement membranes and in the glomerular capsule, but as far as the glomerular tuft is concerned merely mentioned the occurrence of "crescentic deposits of sudanophilic material in Bowman's space" without discussing other characteristics of this material.

The morphological description of the hyaline-fibrinoid material in various locations will be followed by a discussion of its relationship to hyaline arteriolar sclerosis and tubular casts of inspissated protein as well as to other renal lesions of diabetes. The etiology of the hyaline-fibrinoid lesions will also be discussed.

7. Kimmelstiel, P., and Wilson, C.: Benign and Malignant Hypertension and Nephrosclerosis, Am. J. Path. **12**:45-82, 1936.

8. Fahr, T.: Ueber Glomerulosklerose, Arch. path. Anat. **309**:16-33, 1942.

9. (*a*) Spühler, O.: Die diabetische Glomerulosklerose, Helvet. med. acta **11**:27-30, 1944. (*b*) Spühler, O., and Zollinger, H. U.: Die diabetische Glomerulosklerose, Deutsches Arch. klin. Med. **190**:321-379, 1943. (*c*) Zollinger, H. U.: Die diabetische Glomerulosklerose, Schweiz. med. Wchnschr. **73**:1432-1434, 1943.

10. Wernly, M.: La Glomérulosclérose diabétique, Rev. méd. Suisse Rom. **64**:615-632, 1944.

11. Hall, G. F. M.: The Significance of Atheroma of the Renal Arteries in Kimmelstiel-Wilson's Syndrome, J. Path. & Bact. **64**:103-120, 1952.

12. Barrie, H. J.; Aszkanazy, C. L., and Smith, G. W.: More Glomerular Changes in Diabetics, Canad. M. A. J. **66**:428-431, 1952.

13. Simon, M. A.: The Nephrotic Syndrome with Hypertension in Diabetes Mellitus, Canad. M. A. J. **43**:425-430, 1940.

14. Allen, A. C.: So-Called Intercapillary Glomerulosclerosis: A Lesion Associated with Diabetes; Morphogenesis and Significance, Arch. Path. **32**:33-51, 1941; The Kidney: Medical and Surgical Diseases, New York, Grune & Stratton, Inc., 1951.

MATERIAL AND METHODS

The material for the present study was obtained by a screening of 4,400 autopsies on patients of all ages performed at the Kings County Hospital in the years 1945-1950. The kidney slides were reviewed in all cases of known diabetes, uremia, hypertension, glycosuria and hyperglycemia without a history of diabetes, albuminuria, and elevation of nonprotein nitrogen in the blood. A total of 177 autopsies of patients with unquestionable diabetes was thus obtained. Of these, fixed renal tissue was available for detailed study in 15 cases. Paraffin blocks were obtained in an additional 36 cases, and these sections were cut and stained by various methods as needed. Since my interest was concentrated mainly upon the advanced stages of diabetic renal lesions, a disproportionately large number of cases of such lesions, namely 19, was obtained. Fixed tissue was available for study in eight of these. The remaining 32 diabetic cases were equally divided into two groups, one with moderate glomerular lesions of the nodular or diffuse variety and a second with no significant glomerular lesions.

As controls, tissues and blocks from 52 kidneys of nondiabetics were utilized. Forty-four of these were taken from hypertensive patients showing various degrees of arteriolar nephrosclerosis. Six cases of glomerulonephritis and two cases of renal amyloidosis completed this series. Fibrin stains were controlled by staining sections of pneumonic lung and sections of chronic gastric ulcer.

Standard stains used for the present study included hematoxylin and eosin, Goldner's modification of Masson's trichrome stain, and Van Gieson's stain. In addition, the following stains and methods were used as needed: Weigert's fibrin stain; phosphotungstic acid hematoxylin; silver-impregnation methods of Wilder, Bielschowsky, and Gomori; resorcin-fuchsin stain of elastic fibers; Congo-red and methyl-violet stains for amyloid; Sudan IV stain for fat, and 1 per cent solution of toluidine blue for study of metachromasia. Several variants of the periodic acid-Schiff's reaction were also employed [15] without contributing significantly to a better understanding of the problem. A method which was found useful in studying the hyaline-fibrinoid lesion was the silver-impregnation method of Gomori [16] followed by the rapid trichrome reagent of Gomori [17] for 15 minutes. Nuclear stains were not used to avoid unnecessary complication of the morphological picture. The Gomori method outlined exceptionally well the thickened basement membranes of the glomerular tuft, while the remaining glomerular contents were stained green or red, thus permitting an evaluation of the relationship of various structures of the glomerular tuft.

Sections were cut at 6 μ. Additional sections were cut at 4 μ, and serial sections were employed in isolated instances.

MORPHOLOGY OF THE HYALINE-FIBRINOID GLOMERULAR LESION

The observations reported hereafter are based mostly on study of kidneys containing large amounts of the hyaline-fibrinoid material and originating from 18 diabetic patients with advanced stages of renal lesions.

15. McManus, J. F. A.: Histological Demonstration of Mucin After Periodic Acid, Nature, London **158**:202, 1946.

16. Gomori, G.: Silver Impregnation of Reticulum in Paraffin Sections, Am. J. Path. **13**:993-1001, 1937; The Effect of Certain Factors on the Results of Silver Impregnation for Reticulum, ibid. **15**:493-495, 1939.

17. Gomori, G.: A Rapid One-Step Trichrome Stain, Am. J. Clin. Path. **20**:661-664, 1950.

The hyaline-fibrinoid glomerular lesion occurred predominantly in severely damaged kidneys of diabetics. Falling into this category were kidneys showing a considerable degree of glomerular fibrosis and tubular damage with a marked distortion of the renal architecture. In spite of extensive glomerular fibrosis the nodular lesion of diabetes could be identified in 14 cases. In four cases the glomerular lesion was of diffuse type, as described by Bell.[4] Characteristically, the glomeruli with either type of lesion, although severely damaged, were of normal size or were actually larger than normal. These lesions were inevitably associated with arterial and arteriolar sclerosis, usually advanced. Inflammation, in the form of focal chronic pyelonephritis, was present in only one case.

In routine sections of such kidneys, stained with hematoxylin and eosin, it was possible to discern in peripheral portions of the more-or-less altered glomerular tufts the presence of a highly eosinophilic, glossy material with a faint bluish hue (Fig. 1). This material assumed the appearance of crescents or round or oval masses which were completely acellular. Fine to coarse vacuoles were frequently present. On closer scrutiny smaller fragments of similar material could be seen in various locations within the thickened loops of the glomerular tuft. In this staining technique the hyaline-fibrinoid lesion could be distinguished from the nodular lesion by its more marked eosinophilia and strikingly homogenous appearance, but admittedly such differentiation may be difficult. On the other hand, the hyaline-fibrinoid lesions acquired a vivid-red color in trichrome stain, which is therefore more suitable for study of the lesions in detail.

In Goldner's modification of Masson's trichrome stain the hyaline-fibrinoid material stood out in the form of brilliant-red glomerular masses (Fig. 2). These gave the impression of dense coagula arranged in the form of crescents or globules found predominantly at the periphery of the glomeruli and bulging into Bowman's space (Fig. 3). In extreme cases a partial or almost-complete transformation of a glomerular tuft into a mass of trichrome-red material could be observed (Fig. 4). According to the manner in which the section was cut, the deposits might appear as isolated from the main body of the glomerular tuft or as part of it. Consecutive sections always revealed that the material constituted part of the tuft. A frequent artefact was splitting of the larger masses into two or more parts, probably due to great fragility of the material (Figs. 1 and 2).

The problem which gave greatest concern was the location of the material in relation to the structural elements of the glomerulus.

It was evident that the material was not located in Bowman's space, since the hyaline-fibrinoid lesions were frequently covered by a well-preserved visceral layer of Bowman's capsule and separated by a narrowed but empty subcapsular space from the parietal layer of cells (Fig. 1). In some glomeruli, however, adhesions between the two layers tended to obscure this relationship.

Since the hyaline-fibrinoid material was found predominantly in at least partially altered glomeruli with impaired blood supply, we experienced great difficulty in trying to establish whether it was located in the lumen of the capillaries or in their walls.

The smallest deposits of trichrome-red material were frequently found in the form of small peripheral knobs which lifted the visceral layer of Bowman's capsule (Fig. 4). Usually no capillary lumen could be found in or around these masses. Only occasionally could one definitely determine that the material was located in

the walls of capillaries (Figs. 4 and 6). The lumina of such capillaries were usually narrowed by thickened surrounding walls, and the presence of red blood cells in these altered vessels was exceptional.

In a search for a method which would contribute to a better understanding of this problem, various periodic acid-Schiff reagent methods were tried, to no avail, since the distinction between the basement membranes of the glomerulus and

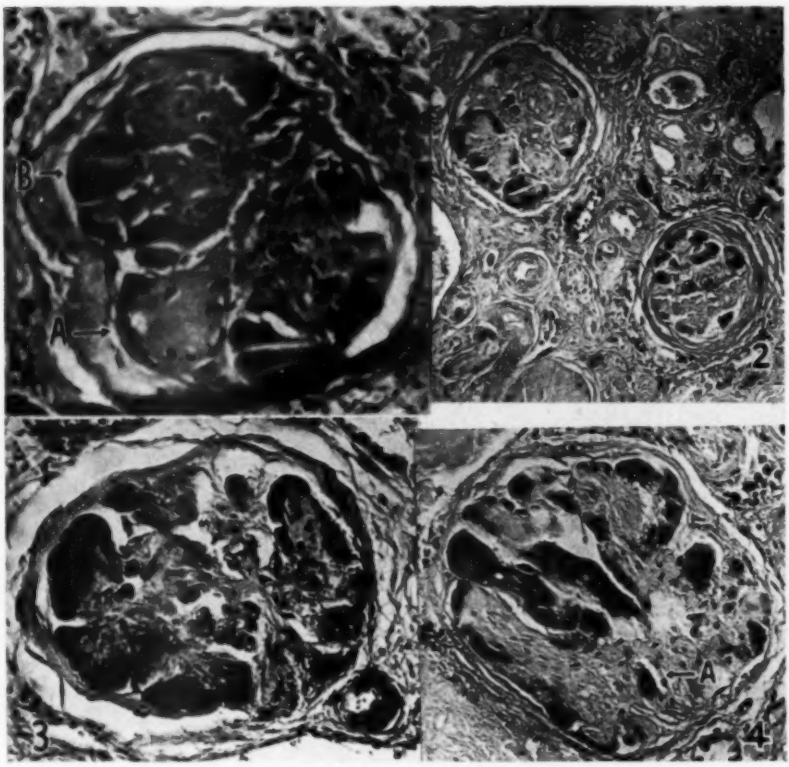

Fig. 1.—Hematoxylin and eosin stain; diabetic kidney. Large glomerulus showing a well-developed nodular lesion (*A*) and several hyaline-fibrinoid lesions (*B*). The latter are characterized by a smooth, homogenous, strikingly eosinophilic appearance and are frequently split into smaller fragments. An intact visceral layer of Bowman's capsule surrounds some of the lesions; × about 200.

Fig. 2.—Goldner's modification of Masson's trichrome stain; diabetic kidney. Dark crescents are located around the periphery of nodular glomerular lesions. They represent the intensely-red-staining, glossy, hyaline-fibrinoid material; × about 100.

Fig. 3.—Goldner's modification of Masson's trichrome stain; diabetic kidney. The dark areas represent the crescents and balls of red-staining hyaline-fibrinoid material. Note similar staining of the hyaline in a sclerotic arteriole; × about 250.

Fig. 4.—Goldner's modification of Masson's trichrome stain; diabetic kidney. There are large deposits of hyaline-fibrinoid material. At *A* the material is seen in the wall of a patent but empty capillary loop. Peripheral small deposits in the form of peripheral knobs can also be noted; × about 250.

the hyaline-fibrinoid material was not sufficiently clear. Use of Gomori's silver-impregnation method followed by his rapid trichrome reagent proved more useful (Fig. 7).

The hyaline-fibrinoid material was surrounded by thin membranous structures taking the stain of reticulum fibers. These membranes demarcated spaces of various sizes, which either followed the course of glomerular capillaries or were markedly

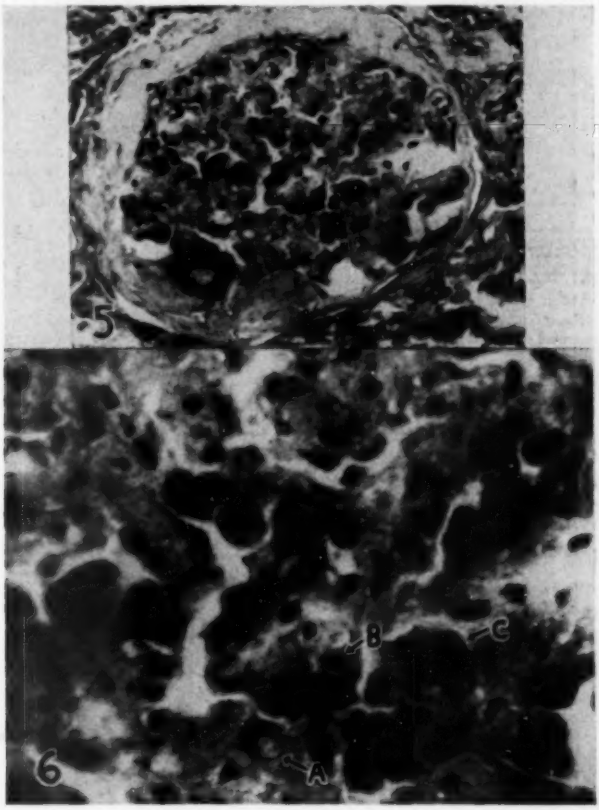

Fig. 5.—Goldner's modification of Masson's stain; diabetic kidney. Glomerulus with many small dark, in reality red, deposits of hyaline-fibrinoid material; × 200.

Fig. 6.—Same glomerulus as that in Figure 5, × 400. At *A* there is deposition of hyaline-fibrinoid material in the wall of a capillary. At *B* there is partial and at *C* complete occlusion of the capillary lumen by this material. At *C* it is impossible to differentiate the material from a hyaline capillary thrombus. Note that the material in this and other locations is covered by the visceral layer of Bowman's capsule.

distorted by adhesions. In this staining technique as well as in trichrome stain one could notice that the spaces were formed by splitting of the capillary wall (Fig. 8). Some of these spaces were filled with hyaline-fibrinoid material; others contained pale-blue-staining masses. Transitions between these two variously staining com-

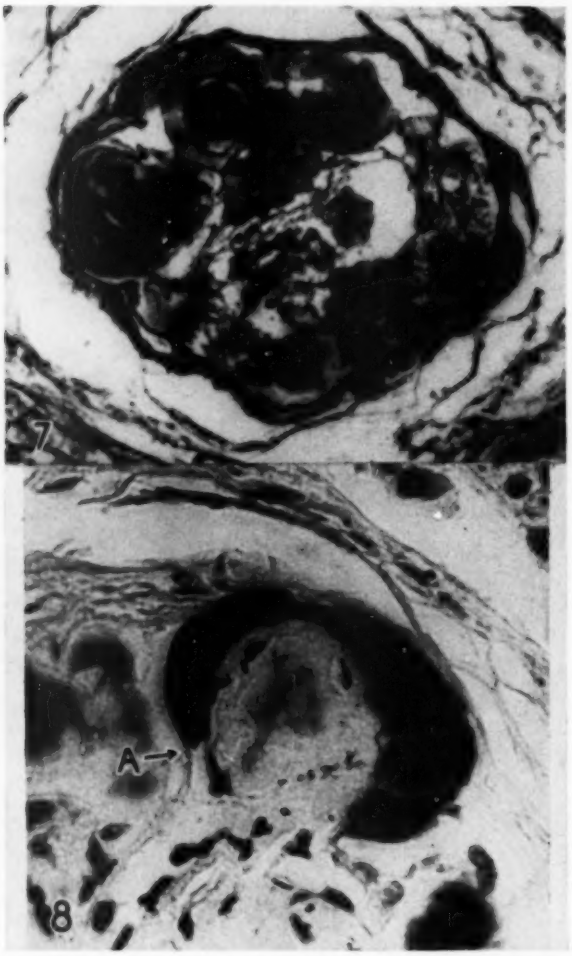

Fig. 7.—Gomori's silver impregnation followed by rapid trichrome reagent; diabetic kidney. The nodular diabetic lesions appear black and have a fibrillar structure. One of them is surrounded by a gray band of tissue, which represents the hyaline-fibrinoid material and in reality stains intense red. The hyaline-fibrinoid material is surrounded by argentophilic membranes of various thickness. Between the crescent of hyaline-fibrinoid material and the smaller nodular lesion there is an almost circular space, which represents a partly obliterated capillary. Note various shades of gray within the glomerular tuft. This material stains various shades of red, and some of it stains pale green; × 240.

Fig. 8.—Goldner's modification of Masson's trichrome stain; diabetic kidney. A nodular diabetic lesion surrounded by a crescent of hyaline-fibrinoid material. The wall of a capillary vessel seen on the left splits in *A* to encompass the hyaline-fibrinoid mass. The split is not as clearly seen on the opposite end of the hyaline-fibrinoid mass; × 475.

ponents were frequent. The crescentic peripheral deposits of hyaline-fibrinoid material frequently surrounded the typical nodular lesions of diabetes. The former could be readily distinguished from the latter because the nodular lesions were markedly argentophilic in this staining technique, whereas the hyaline-fibrinoid lesions took an intense-red stain and were merely surrounded by a thin layer of argentophilic material. Between the two lesions a narrow space could be readily observed in many instances. This space most likely represented a markedly narrowed lumen of the capillary loop which customarily surrounds the nodular lesion. Very occasionally a red blood cell could be found in this space separating the two lesions (Fig. 7). The possibility of an artefact with formation of the narrow, slit-like space due to shrinkage of tissues was considered. However, the frequent occurrence of such morphological arrangement in material originating from various sources has led to the conclusion that the space actually exists. In other instances the hyaline-

TABLE 1.—*Differential Staining Properties of the Nodular Lesions of Kimmelstiel-Wilson and of the "Hyaline-Fibrinoid" Glomerular Lesion*

Stain	Nodular Lesion	"Hyaline-Fibrinoid" Lesion
1. Hematoxylin and eosin	Eosinophilic	Intensely eosinophilic, glossy, with faint bluish hue
2. Masson's trichrome (Goldner's modification)	Green, occasionally small portions red	Intense red
3. Weigert's fibrin stain	Faint blue, fibrillar	Intense blue-purple (occasionally only in foci)
4. Phosphotungstic acid hematoxylin	Yellow	Blue-purple (occasionally only in foci)
5. Van Gieson	Reddish to red	Yellow
6. Periodic acid-Schiff reagent methods	Red, fibrillar	Red, homogenous
7. Bielschowsky's silver impregnation	Argentophilic, black or dark brown, fibrillar	Argentophilic, brown, smooth
8. Wilder's reticulum stain	Argentophilic, fibrillar	Light brown, smooth
9. Gomori's reticulum stain followed by rapid trichrome reagent	Intensely argyrophilic, fibrillar, mostly black	Intensely red, surrounded by thin argentophilic membranes
10. Sudan IV	Fat absent	Fat present
11. Toluidine blue	No metachromasia	Occasional, faint metachromasia
12. Stains for amyloid	Negative	Negative

fibrinoid material could be seen in the form of broad bands of tissue surrounding a lumen, which appeared to be that of a narrowed capillary. All these observations led to the conclusion that the material was located in the walls of capillaries rather than in the lumina. It should be added that frequently it was very difficult to determine the location of the material from morphological observations. It is possible that complete occlusion of the capillary lumen by hyaline-fibrinoid material may occur, as it can also occur in the hyaline form of arteriolar sclerosis. Under these circumstances the question of location of the hyaline-fibrinoid material in the lumen or in the wall of the capillaries and its differentiation from a hyaline capillary thrombus cannot be answered (Figs. 5 and 6).

MORPHOLOGY OF THE HYALINE-FIBRINOID GLOMERULAR LESIONS COMPARED WITH THE NODULAR LESIONS OF DIABETES

There appears to be little doubt that the hyaline-fibrinoid glomerular lesions have frequently been confused with the nodular diabetic lesions because of the great frequency with which they occur together in the same kidney or in the same glomerulus and because they occasionally assume the same globular or oval shape.

The size of the two lesions may also be similar. If the staining characteristics of the two lesions appeared confusing in hematoxylin and eosin stain, the differences were striking in other staining techniques (Table 1). Whereas the nodular lesion usually gave the staining reactions of connective tissue, the hyaline lesion had the staining properties of the so-called fibrinoid. The latter properties include positive staining for fibrin in the Weigert (Fig. 9) and phosphotungstic acid hematoxylin techniques (Fig. 10) and a yellow color in Van Gieson stain. Whereas small deposits of hyaline-fibrinoid material were usually free of fat, the larger deposits often had

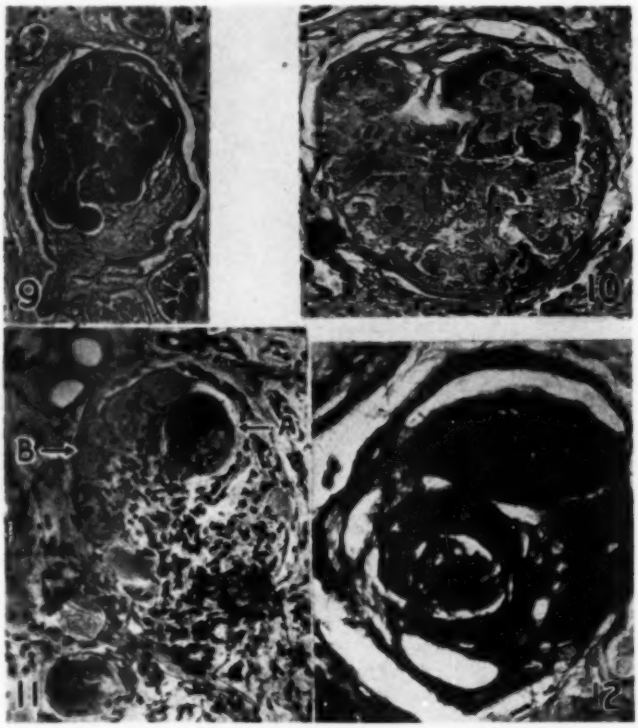

Fig. 9.—Weigert's fibrin stain; diabetic kidney. A glomerulus the tuft of which has been almost completely transformed into hyaline-fibrinoid material which takes the intense-blue stain of fibrin; × 175.

Fig. 10.—Phosphotungstic acid hematoxylin stain; diabetic kidney. Dark areas represent crescents of hyaline-fibrinoid material staining intense blue-purple, in a fashion identical with fibrin. Smaller deposits are seen throughout the glomerulus; × 250.

Fig. 11.—Frozen section, Sudan IV stain; diabetic kidney. Crescent of intensely sudanophilic hyaline-fibrinoid material surrounding a nodular lesion which is free of fat (*A*). Note the relative absence of fat in smaller peripheral deposits of hyaline-fibrinoid material (*B*). Fat is abundant in sclerotic arterioles; × 175.

Fig. 12.—Periodic acid-fuchsin stain after McManus; diabetic kidney. A nodular lesion characterized by fibrillar structure can readily be distinguished from two broad bands of homogenous hyaline-fibrinoid material which show the frequent artefact of splitting into several smaller portions; × 250.

a high fat content. The lipids were found in the form of globules or were finely dispersed, giving a diffuse red stain with Sudan IV (Fig. 11). Under the polarizing microscope a portion of the glomerular lipids appeared doubly refractile. In contrast, fat was present in insignificant amounts in the nodular lesions. Affinity for silver was present in both lesions in Bielschowsky's staining technique. However, the nodular lesion was usually black and finely fibrillated, whereas the hyaline-fibrinoid lesion assumed a brownish, smooth, homogenous appearance. In silver-impregnation methods for reticulum the nodular lesion preserved its argentophilic properties, whereas the hyaline-fibrinoid lesion remained faintly stained (Fig. 7). In periodic acid techniques both lesions stained red, but the fibrillated appearance of the nodular lesion distinguished it from the smooth hyaline-fibrinoid lesion (Fig. 12). The nodular lesion could also be distinguished from the hyaline-fibrinoid lesion by its greater cellularity. Scattered nuclei could be noticed within the nodular lesion, whereas the hyaline-fibrinoid lesion was completely acellular (Fig. 1).

Another point of differentiation is seen in the natural history of the two lesions. The nodular lesion frequently originates in an otherwise intact glomerulus and may be surrounded by thin-walled capillaries. The latter point has been emphasized in the literature [18] and was apparent in my experience. The hyaline-fibrinoid lesions were never found in intact glomeruli. They appeared only in damaged, altered glomeruli with capillary walls revealing at least some degree of thickening and fibrosis.

HYALINE-FIBRINOID MATERIAL IN OTHER THAN GLOMERULAR LOCATIONS

Deposits of hyaline-fibrinoid material in the parietal layer of the glomerular capsule have been repeatedly described in the literature.[19] These lesions usually appeared in thickened, fibrosed capsules and took the form of shorter or longer linear deposits with focal, knob-like thickenings (Fig. 13). The similarity of these capsular lesions to the lesions of the glomerular tuft was enhanced by the appearance of fibrils giving a positive stain for reticulum in the altered capsules. These fibrils surrounded the hyaline-fibrinoid deposits in a manner similar to that described for the glomerular tufts. An artefact occasionally noted consisted of a portion of hyaline-fibrinoid material attached to the parietal layer of Bowman's capsule. Such structures appeared to be the result of broken adhesions between the tuft and capsule. Similar structures have recently been described in the literature under the term "capsular drops." [12]

Hyaline-fibrinoid lesions located in the basement membrane of the proximal convoluted tubules have been noted in the literature.[20] These lesions were found in 3 of 19 cases of advanced diabetic nephrosclerosis. They had the appearance of fusiform swellings surrounded by fibrils giving a positive stain for reticulum (Fig. 14). As far as could be determined by the methods employed, such lesions were not encountered in the distal portions of the tubules.

The hyaline-fibrinoid change was practically always associated with marked arterial and arteriolar sclerosis. The arteriolar lesions often involved the efferent as well as the afferent arterioles. Without any special study of this problem, it

18. Spühler and Zollinger.[9] Allen.[14]

19. Kimmelstiel and Wilson.[1] Murakami.[2] Spühler and Zollinger.[9] Allen.[14]

20. Fahr.[8] Spühler and Zollinger.[9] Allen.[14]

Fig. 13.—Goldner's modification of Masson's trichrome stain; diabetic kidney. There is an accumulation of hyaline-fibrinoid material in Bowman's capsule. The lesion is fusiform and stained intense red. Compare this staining with the identical staining qualities of the hyaline sclerotic arteriole and of small foci of hyaline-fibrinoid material present in the glomerular tuft; × 180.

Fig. 14.—Goldner's modification of Masson's trichrome stain; diabetic kidney. There are deposits of red, hyaline-fibrinoid material in the form of fusiform swelling of the basement membrane of convoluted tubules; × 430.

Fig. 15.—Goldner's modification of Masson's trichrome stain; diabetic kidney. Tubular casts of inspissated protein and glomerular deposits of hyaline-fibrinoid material have taken an identical intense-red, glossy stain which appears dark in the photograph; × 85.

appeared that the efferent arteriolar sclerosis was somewhat more frequent in the diabetic kidneys than in the control group, an observation corresponding to the findings of Allen.[14]

In hematoxylin and eosin stain the arteriolar lesions were those of hyaline sclerosis, frequently very severe. In other stains the hyaline material found in the arterioles, like the hyaline-fibrinoid lesion, often showed the various staining characteristics of fibrin, including vivid red in trichrome stain (Fig. 3), dark blue in Weigert's fibrin and phosphotungstic acid hematoxylin stains, and yellow in Van Gieson stain. An additional similarity was the presence of large amounts of fat in advanced stages of both lesions (Fig. 11). Marked narrowing and almost complete occlusion of arteriolar lumina by masses of hyaline material was occasionally observed in severely damaged diabetic kidneys.

Tubular casts of inspissated protein frequently displayed staining characteristics similar to if not identical with those of the hyaline-fibrinoid lesions and the hyaline material of arteriolar sclerosis (Fig. 15). These features were particularly well seen in the central portions of hyaline casts, whereas the peripheral portions usually stained in a somewhat different manner. Thus the central portions of casts usually stained red in trichrome stain, whereas the periphery stained pale green. The core of the casts stained intense blue in phosphotungstic acid hematoxylin stain, whereas the periphery stained yellow. In silver-impregnation methods the central portion of the casts usually displayed a somewhat more intense argentophilia than the periphery. It is suggested that the staining differences may be due to a difference in concentration of the material, the denser central portion having preserved the staining properties of precipitated protein, including that of metachromasia with toluidine-blue solution.[21]

ESSENTIAL CLINICAL DATA ASSOCIATED WITH HYALINE-FIBRINOID LESIONS OF DIABETES

The 18 patients with moderate and high amounts of the hyaline-fibrinoid substance in the glomeruli comprised 13 women and 5 men. One woman was only 28 years of age, with a history of diabetes since the age of 13. The remaining 17 patients varied in age from 48 to 78, the average age being 60.7. The known duration of diabetes in 9 cases varied from 1½ to 27 years, with an average of 14.2 years. In six additional cases the diabetes was of "many years' duration. In four cases the duration of the disease was unknown.

The severity of the diabetes, as judged by insulin coverage, offered data of interest. Seven patients did not require insulin at any time. Three required from 10 to 30 units daily. In 8 a significant diminution in the insulin requirement was noted. The drop was most significant in a 48-year-old man who had been diabetic for 23 years and originally required 65 units of protamine zinc insulin and 35 units of regular insulin daily to control his diabetes. During the year preceding his death, his insulin requirements dropped to 16 units of the former and 8 units of the latter. Prior to death the patient went into a hypoglycemic coma after having taken his normal amount of insulin. During the last two months of his illness his fasting blood sugar values never went above 105 mg. per 100 ml. In the entire group of

21. Oliver, J.: New Directions in Renal Morphology: A Method, Its Results, and Its Future, Harvey Lect. (1944-1945) **40**:102-155, 1945.

18 patients only one instance of diabetic acidosis occurred, although diabetic acidosis was found with considerably greater frequency in our entire series of diabetics.

These observations bear out findings by Wernly,[10] McManus,[22] Zubrod, Eversole, and Dana,[23] and others [24] who have also noticed a diminution of insulin requirements and rarity of acidosis in patients with severe renal damage.

All 18 cases showed morphological evidence of severe renal damage. However, the corresponding clinical data were available for only 12 patients. Of these, eight died in uremia and four showed evidence of impaired renal function with increase in blood levels of urea and creatinine. Seven of eight patients with uremia had a rapid downhill course with a duration varying between three months and three years from the onset of the impairment of renal function. Severe albuminuria was present in 12 patients, 1 had a trace of albumin in the urine, and no information was available for 5. Information on edema was available for 15 patients; 3 had none, 2 had slight edema, 8 had moderate edema, and 2 had severe generalized edema.

Information on blood pressure, past and present, was available in 17 cases. One patient, the 28-year-old woman, had normal blood pressure. Two patients were admitted in extremis, and their blood pressure was below normal. Fifteen had definite hypertension of various durations.

Cholesterol blood levels were determined in six cases and varied between 200 and 296 mg. per 100 ml., the average being 249 mg. Funduscopic examination was carried out in four cases; all patients showed fundal hemorrhages and exudates. In three additional cases cataracts were present.

These clinical data are essentially similar to those presented as characteristic for the Kimmelstiel-Wilson syndrome. Of particular significance is the observation that the seemingly mild forms of diabetes may in reality represent a drop in insulin requirements and blood sugar level in diabetics previously having had severe forms of the disease. Of interest also is the rapid downhill course of patients dying of renal insufficiency.

COMMENT

Specificity of the Hyaline-Fibrinoid Material.—A. Glomeruli: In an endeavor to evaluate the specificity of the hyaline-fibrinoid lesion a table was compiled (Table 2) comparing quantitatively the amounts of the material in the kidneys of diabetics and of nondiabetic controls. It is obvious that the hyaline-fibrinoid lesion is not absolutely specific for diabetes but occurs also in other morbid states.

The quantitative evaluation is based on entirely subjective criteria; the kidneys were accordingly classified into four categories, as shown in the table. In my estimates I have attempted to take into consideration the amount of hyaline-fibrinoid material found in individual glomeruli and also the number of glomeruli involved. Admittedly, this is an inaccurate way of estimating the lesion, but it appears sufficient for purposes of comparison.

22. McManus, J. F. A.: Medical Diseases of the Kidney: An Atlas and Introduction, Philadelphia, Lea & Febiger, 1950.

23. Zubrod, C. G.; Eversole, S. L., and Dana, G. W.: Amelioration of Diabetes and Striking Rarity of Acidosis in Patients with Kimmelstiel-Wilson Lesions, New England J. Med. **245**:518-528, 1951.

24. Wilson, J. L.; Root, H. F., and Marble, A.: Diabetic Nephropathy: A Clinical Syndrome, New England J. Med. **245**:513-517, 1951.

Table 2 shows that the hyaline-fibrinoid lesion occurred with a much greater frequency in kidneys of diabetics than in the control group. As a matter of fact, high degrees of involvement were seen only in cases of severe renal damage associated with diabetes. In this entire group of 51 diabetic cases the lesion occurred in moderate degree in 13 cases and in high degree in 11. On the other hand, the lesion was found in 18 of 19 cases of advanced diabetic nephrosclerosis. In the kidneys with less advanced damage the hyaline-fibrinoid lesion was usually found in areas of focal renal fibrosis.

In the control group of 43 cases of arteriolar nephrosclerosis associated with hypertension but not with diabetes, only 3 revealed the presence of the hyaline-fibrinoid material in moderate amounts. All three were cases of advanced arteriolar nephrosclerosis with severe renal damage. In none of the cases in this control group

TABLE 2.—*Accumulation of Hyaline-Fibrinoid Substance in Glomeruli and Arterioles of Diabetic and Control Kidneys*

Type of Material	Total No. of Cases	In Glomeruli				In Arterioles			
		None	Trace	Moder. Amt.	Large Amt.	None	Trace	Moder. Amt.	Large Amt.
Diabetic glomerular lesions, advanced.....	19	0	1	7	11	0	3	10	6
Diabetic glomerular lesions, moderate.....	16	10	2	4	0	6	0	9	1
No significant diab. glomerular lesions.....	16	12	2	2	0	10	1	3	2
Total diabetic cases.....	51	22	5	13	11	16	4	22	9
Arteriolar nephrosel., advanced with hyperten.	9	2	4*	3	0	2	1	5	1
Arteriolar nephrosel., advanced with rapid course ("malignant")	9	8†	1†	0	0	0	4†	4†	1†
Arteriolar nephrosel., mod. with hypertension	12	7	5*	0	0	5	1	6	0
Arteriolar nephrosel., mild with hypertension	14	12	2*	0	0	11	1	2	0
Total arteriolar sclerosis, with hypertension	44	29	12*	3	0	18	7	17	2
Glomerulonephritis, intracapillary (lobular).	3	1‡	2†	0	0	3	0	0	0
Glomerulonephritis, subacute and chronic...	3	3	0	0	0	3	0	0	0
Total glomerulonephritis	6	4‡	2	0	0	6	0	0	0
Amyloidosis, renal	2	2	0	0	0	2	0	0	0

* Trace refers mostly to glomeruli undergoing obliteration (see text).
† Fibrin and areas of necrosis and inflammation have been excluded from the count wherever the identity of such lesions could be established beyond doubt.
‡ Hematoxylin and eosin stain only available in one case.

was a large amount of the hyaline-fibrinoid material found. The hyaline-fibrinoid material in glomeruli of nondiabetics was usually found in the form of globular masses. The crescentic form of the deposits, corresponding to the course of the capillaries around the nodular lesion, was not found in the control series.

In central portions of glomeruli undergoing obliteration in association with arterial or arteriolar nephrosclerosis, occasional presence of trichrome-red material was noted. It appears to us that this material represents altered staining characteristics of the remnants of the glomerular tuft rather than accumulation of the hyaline-fibrinoid material. However, in order to avoid any possible error, we have classified these cases in the category "trace," since the accumulation of this trichrome-red material was never considerable.

The nine cases of malignant nephrosclerosis showed focal deposits of fibrin in and around areas of glomerular necrosis. Fibrin differs from the hyaline-fibrinoid

material by formation of definite strands and fibrils, whereas the latter is smooth and homogenous. The granular appearance of areas of acute glomerular necrosis, even in the absence of morphologically recognizable fibrin, is different from the homogenous, smooth, coagulum-like appearance of the hyaline-fibrinoid lesions. For these reasons and also because of the associated evidence of inflammation, invariably lacking in the diabetic kidneys, the presence of fibrin or acute necrosis was not included in the data. However, whenever the identity of such lesions could not be morphologically established beyond doubt, they were included in the table.

Similarly, accumulation of fibrin in the glomeruli and inflammatory crescents in cases of glomerulonephritis was, if possible, excluded from the data, since I do not consider the hyaline-fibrinoid material as identical with fibrin. In only two of six cases of glomerulonephritis were small amounts of the hyaline-fibrinoid material present in the glomeruli.

Two cases of amyloidosis did not show any hyaline-fibrinoid material. It is, however, of interest to point out the similarity of distribution of the amyloid and of the hyaline-fibrinoid material.

B. Arterioles: As pointed out, the arterioles in the kidneys of diabetics frequently contain material with staining reactions identical with those of the hyaline-fibrinoid glomerular lesions. A quantitative comparison of these arteriolar lesions in diabetic and in nondiabetic kidneys appeared desirable.

Table 2 shows that moderate amounts of the hyaline-fibrinoid material may be found quite frequently in arteriolar hyaline sclerosis not associated with diabetes. However, the incidence of a severe degree of this type of arteriolar involvement is higher in diabetics. Whereas large amounts of hyaline-fibrinoid substance were found in only 2 of 43 cases of arteriolar sclerosis not associated with diabetes, this type of lesion was found in 9 of 51 diabetic kidneys. This finding substantiates the statement [25] that "intimal disease of small arteries is definitely more severe in diabetics than in nondiabetics."

C. Other Sites: Hyaline-fibrinoid lesions of the parietal layer of Bowman's capsule and of the basement membrane of the tubules was not found in our control series and appears to be associated exclusively with diabetes.

It would appear, then, that the specificity for diabetes of the glomerular and arteriolar hyaline-fibrinoid lesions is quantitative rather than qualitative. However, the crescentic shape of hyaline-fibrinoid glomerular deposits as well as the simultaneous occurrence of the hyaline-fibrinoid lesions in various locations, i. e., in the glomeruli, arterioles, glomerular capsules, and tubular membranes, appear to characterize diabetes mellitus.

The Mechanism of Formation and the Nature of the Hyaline-Fibrinoid Glomerular Lesions.—The study of renal tissue in Gomori's reticulum stain followed by his rapid trichrome reagent [26] gave important clues as to the possible morphogenesis of the hyaline-fibrinoid lesions.

25. (*a*) Bell.[4] (*b*) Bell, E. T., and Clawson, B. J.: Primary (Essential) Hypertension: Study of 420 Cases, Arch. Path. **5**:939-1002, 1928.

26. Gomori, footnotes 16 and 17.

This staining method outlines the basement membranes of normal glomeruli very faintly except in the vicinity of the hilum. With progressing glomerular fibrosis, focal or diffuse, the basement membranes of the glomerular capillaries become thickened and all or parts of them stain more intensely for reticulum. Contrary to the view expressed by Barrie and co-workers,[12] the hyaline-fibrinoid material does not appear in glomeruli with intact basement membranes. With appropriate staining methods the alteration of the basement membrane is always apparent. The fibers of the thickened capillary wall become readily split and frayed. In accordance with the views of Allen,[14] focal accumulation of these thickened, frayed, argentophilic fibers constitutes the nodular lesion of diabetes. In addition, the altered argentophilic fibers of the capillary wall have a considerable tendency toward splitting and formation of adhesions. An occasional observation would suggest that the process of splitting of the capillary wall results in separation of two membranous structures: one corresponding to the endothelial basement membrane and the other to the thin structure supporting the parietal layer of Bowman's capsule. Spaces which are created by this process of splitting are well demarcated by silver-impregnation methods for reticulum and are filled with material which in trichrome stain takes either a faint-blue stain or the vivid-red color of the hyaline-fibrinoid lesion. It is suggested that the bluish material constitutes edema fluid and that appearance of the hyaline-fibrinoid material results from precipitation of the protein fraction of this edema fluid; an appearance of faint metachromasia in some of the hyaline-fibrinoid lesions, similar to that observed in renal casts of precipitated protein,[21] speaks in favor of this mechanism. The concept of a protein nature of the hyaline-fibrinoid material is further supported by the fact that in a variety of staining techniques the hyaline tubular casts, which are assumed to consist mainly of protein,[27] display in their central portions staining characteristics identical with those of the hyaline-fibrinoid material.

A strongly positive periodic acid-leucofuchsin reaction indicates that mucopolysaccharides are probably present in the hyaline-fibrinoid material. A similar process of formation of argentophilic fibers and accumulation of hyaline-fibrinoid material can also be observed in the parietal layer of Bowman's capsule and in the basement membrane of the proximal tubules. This would suggest that a similar pathogenetic process is in operation in these structures as well.

Comparison of Hyaline-Fibrinoid Lesions and Hyaline Arteriolar Sclerosis.—Moritz and Oldt,[28] investigating the staining properties of material accumulating in the walls of arterioles showing the hyaline form of sclerosis, stated that the staining reaction of these lesions is predominantly blue in azocarmine and green with Masson's trichrome stain. Although some of the hyaline sclerotic arterioles indeed stain in this fashion, it has been my experience that the hyaline material in the majority of hyaline arterioles in severely damaged diabetic kidneys and in some nondiabetic kidneys stains red with Masson's trichrome and also possesses other staining characteristics of the hyaline-fibrinoid material.

Observations of arteriolar lesions of the hyaline type showing staining reactions comparable to those of the hyaline-fibrinoid material are infrequent in the litera-

27. Addis, T.: The Renal Lesion in Bright's Disease, Harvey Lect. **23**:222-250, 1929.

28. Moritz, A. R., and Oldt, M. R.: Arteriolar Sclerosis in Hypertensive and Non-Hypertensive Individuals, Am. J. Path. **13**:679-728, 1937.

ture. Herxheimer [29] and Matsuno [30] were probably the first to notice such change in hyaline arteriolosclerosis of the vessels of the spleen. Lange [31] pointed out a similar staining reaction in the early stages of the arteriosclerotic process of the larger vessels. A number of investigators have discussed similar changes in arterioles of the brain in hypertension,[32] and terms like arteriolonecrosis [32a] and hyalinosis [32d] have been applied to differentiate these lesions from other forms of arteriolar sclerosis.

Schürmann and MacMahon [33] stated that the trichrome-red hyaline change is found in severely damaged renal arterioles. They did not consider this change as equivalent to arteriolar necrosis unless some other evidence of necrosis was found, such as permeation with blood or an inflammatory reaction. These observations coincide with my own. Appearance of the hyaline-fibrinoid material in the walls of damaged arterioles in a significant amount is an indication of the severity of the arteriolosclerotic process, and it is found mostly in severely damaged kidneys. This change is particularly marked in advanced stages of arteriolar hyaline sclerosis associated with diabetes. It has been noticed that the hyaline arteriolar lesions commence with accumulation of droplets of foreign material in the subintimal space of the arterioles. Further increase in the amount of the accumulated material and its spread around the arteriolar lumen help give the arterioles the characteristic appearance of hyaline-fibrinoid sclerosis with a thick layer of homogenous, markedly eosinophilic material accumulating in the subintimal space. A reticulum stain reveals that the material is lined inward and outward by thin membranes giving a positive stain for reticulin fibrils. It would be beyond the scope of this paper to enlarge further on the mechanism of formation of hyaline arteriolar sclerosis. These few remarks are intended only to emphasize the similarity of this type of arteriolar sclerosis and the hyaline-fibrinoid lesions of diabetic kidneys.

Similar staining characteristics of the material, a similar relationship to fibrils taking the reticulum stain, and, possibly, a similar pathogenesis all suggest very strongly that accumulation of the hyaline-fibrinoid material is the equivalent of arteriolar hyaline sclerosis. It appears, therefore, that factors causing arteriolar hyaline sclerosis may extend their action, particularly in cases of diabetes mellitus, upon other structures, specifically the glomerular tuft and the proximal portion of the basement membranes of the nephron.

29. Herxheimer, G.: Über das Verhalten der kleinen Gefässe der Milz, Berl. klin. Wchnschr. **54**:82-84, 1917.

30. Matsuno, G.: Über Wandveränderungen der kleinen Milzarterien, Arch. path. Anat. **240**:69-80, 1923.

31. Lange, F.: Studien zur Pathologie der Arterien, insbesondere zur Lehre von der Arteriosklerose, Arch. path. Anat. **248**:463-604, 1924.

32. (*a*) Lindemann, H.: Die Hirngefässe in apoplektischen Blutungen, Arch. path. Anat. **253**:27-44, 1924. (*b*) Rühl, A.: Atherosklerotische Gefässruptur oder Spasmus als Ursache der apoplektischen Gehirnblutung? Beitr. path. Anat. **78**:160-186, 1927. (*c*) Staemmler, M.: Über Veränderungen der kleinen Hirngefässe in apoplektischen und traumatischen Erweichungsherden und ihre Beziehungen zur traumatischen Spätapoplexie, Beitr. path. Anat. **78**:408-429, 1927. (*d*) Anders, H. E., and Eicke, W. J.: Die Gehirngefässe beim Hochdruck, Arch. Psychiat. **112**:1-44, 1940.

33. Schürmann, P., and MacMahon, H. E.: Die maligne Nephrosklerose, zugleich ein Beitrag zur Frage der Bedeutung der Blutgewebsschranke, Arch. path. Anat. **291**:47-218, 1933.

Concept of Pathogenesis of Hyaline-Fibrinoid Lesions.—Investigating the mechanism of formation of hyaline arteriolar sclerosis, Hueck [34] and Jores [35] stated that an alteration of the ground substance of the arteriolar wall precedes its permeation with blood plasma. They were joined by Anitschkow,[36] who furnished experimental evidence that the presence of coagulated proteins in the walls of vessels accounts for the characteristic appearance of hyaline arteriosclerosis. Schürmann and MacMahon [33] suggested that permeation of the arteriolar wall with plasma proteins takes place when there is a disturbance in the functioning of a barrier normally protecting the tissues from intimate contact with blood plasma. They referred to this disturbance as *Dysorie.*

The widespread accumulation of the hyaline-fibrinoid material in the kidneys in diabetes mellitus—its presence in the subintimal space of the arterioles, in the walls of the capillary loops of the glomerular tuft, in Bowman's capsule, and in the basement membrane of the tubules—indicates that the process involves many of the limiting membranes of the kidneys. Whether the process is actually one of permeation of these structures with elements of blood plasma or, as some have advocated,[9b] a product of focal "fibrinoid degeneration" of these structures due to associated infection may be difficult to decide for the time being. In the material investigated inflammation seemed to play an insignificant role. The hyaline-fibrinoid material appears to have a similar if not identical chemical composition as the tubular casts of inspissated protein; the latter certainly represent the product of filtration of blood plasma into the tubules. Therefore it is suggested that the hyaline-fibrinoid changes are the result of permeation of various tissues with protein material originating in blood plasma. The consistent presence of albuminuria in this form of renal involvement suggests that the permeability of the glomerular capillaries is increased. It is conceivable that because of thickening and splitting of the capillary wall components of blood plasma do not filter through but are retained in the spaces created within it. Subsequent alteration of the protein fraction constitutes the hyaline-fibrinoid lesion. It is possible that a somewhat similar pathogenetic process is in operation in hyaline arteriolar sclerosis.

Fatty Deposits and Diabetic Renal Lesions.—It does not seem probable that deposition of fat in the kidney has anything to do with the origin of the hyaline-fibrinoid lesion or, for that matter, with the origin of the nodular lesions in glomeruli of diabetics. Fat is absent in small, early lesions of the hyaline-fibrinoid type and appears in considerable amount only in larger lesions, in glomeruli which have apparently become completely obsolete. As a matter of fact, appearance of fat in the glomeruli of diabetic kidneys in any considerable amount is a chronologically late phenomenon generally associated with the presence of hyaline-fibrinoid material; it is therefore seen mostly in severely damaged kidneys. In less altered renal material, particularly when the glomerular lesion is still confined to the presence of discrete nodules, there is little fat in the glomerular tuft. It would appear, there-

34. Hueck, W.: Anatomisches zur Frage nach Wesen und Ursache der Arteriosklerose, München. med. Wchnschr. **67**:535-538, 573-576 and 606-609, 1920.

35. Jores, L.: Hyaline Degeneration der Arteriolen, in Henke, F., and Lubarsch, O., editors: Handbuch der Speziellen Pathologischen Anatomie und Histologie, Vol. 2, Berlin, Julius Springer, 1924.

36. Anitschkow, N.: Experimental Arteriosclerosis in Animals, in Cowdry, V., editor: Arteriosclerosis: A Survey of the Problem, New York, The Macmillan Company, 1933.

fore, that the "presence of inordinately large amounts of glomerular fat," considered by Wilens, Elster, and Baker [37] as of primary importance in development of the lesions of intercapillary glomerulosclerosis, is a secondary rather than a primary phenomenon and has little if any bearing upon the development of the nodular diabetic lesion. It is of interest that Bloor [38] considered hyperlipemia as a secondary phenomenon in diabetes.

Hyaline-Fibrinoid Lesions and the Origin of Nodular Lesions.—We have attempted to demonstrate that the nodular lesion of Kimmelstiel and Wilson and the hyaline-fibrinoid glomerular lesion, in spite of certain apparent similarities in hematoxylin and eosin stain, are distinct. It is probable that two independent sets of factors influence their formation.

The hyaline-fibrinoid glomerular lesion resembles in all respects hyaline arteriolar sclerosis. However, the involvement of the glomerular tuft by hyaline-fibrinoid material is characteristic, since the arteriolar sclerotic process not associated with diabetes usually does not involve the glomerular capillaries.[39] The extension of the process of sclerosis into the capillaries and accumulation of the hyaline-fibrinoid material seem to account for the large size of sclerotic glomeruli in diabetics. It would thus appear that the walls of glomerular capillaries, even in the presence of many and large nodular lesions, remain capable of a reaction of their own, a reaction similar to that of the arterioles.

The question of intercapillary as opposed to intramural origin of the nodular diabetic lesion has as yet not been satisfactorily resolved. My own observations lead me to believe that the lesion originates in the walls of the capillaries. In this respect these observations coincide with views previously expressed by Allen. It is however, of interest to consider which component of the capillary wall gives rise to the nodular lesion. Jones [40] has recently demonstrated in a very elegant fashion that the glomerular capillary possesses a connective-tissue component in addition to two basement membranes, one belonging to the capillary endothelium and the other to the visceral layer of Bowman's capsule. Jones stressed that the connective-tissue component is not discernible under normal conditions but plays an important part in glomerular inflammation and repair. Jones's views coincide with those expressed by other investigators of the structure of the glomerular tuft, namely Zimmermann [41] and von Möllendorf.[42]

It is improbable that production of voluminous masses of connective-tissue fibers constituting the nodular lesion could take place by simple splitting of the basement membrane without action of some connective-tissue cells. Actually, nodular lesions contain cells within their substance.

37. Wilens, S. L.; Elster, S. K., and Baker, J. P.: Glomerular Lipoidosis in Intercapillary Glomerulosclerosis, Ann. Int. Med. **34**:592-607, 1951.

38. Bloor, W. B.: Biochemistry of the Fatty Acids and Their Compounds, the Lipids, New York, Reinhold Publishing Corporation, 1943.

39. Löhlein, M.: Über Schrumpfnieren, Beitr. path. Anat. **63**:570-632, 1927. Bell and Clawson.[23b]

40. Jones, D. B.: Inflammation and Repair of the Glomerulus, Am. J. Path. **27**:991-1010, 1951.

41. Zimmermann, K. W.: Über den Bau des Glomerulus der menschlichen Niere, Ztschr. mikr. anat. Forsch. **18**:520-552, 1929.

42. Der Exkretionsapparat, in von Möllendorf, W.: Handbuch der mikroskopischen Anatomie des Menschen, Vol. 7: Harn- und Geschlechtsapparat, Pt. 1, Berlin, Springer—Verlag, 1930.

It appears, therefore, that the nodular lesions are formed by focal proliferation of the connective-tissue component of the glomerular-capillary wall; this would account for their staining properties being identical with those of connective tissue.

Hyaline-Fibrinoid Glomerular Deposits and Renal Failure.—The question as to whether accumulation of the hyaline-fibrinoid material in the glomeruli of diabetics plays a role in bringing about renal failure deserves a brief comment. In agreement with Hall,[11] I believe that the vascular damage is likely to be the most prominent factor in the inexorable downhill course of diabetics with sclerotic renal lesions. The appearance of the hyaline-fibrinoid material follows and does not precede the glomerular damage. However, accumulation of the hyaline-fibrinoid material might conceivably accelerate the course of renal deterioration and play a leading role in the characteristically rapid renal failure, the course of which has been clinically compared by some to that of malignant nephrosclerosis.[42]

SUMMARY AND CONCLUSION

A lesion consisting of accumulation of a hyaline material with the staining reactions of fibrinoid in kidneys of diabetics with various degrees of renal sclerosis is described. This material accumulates in the glomerular tufts, glomerular capsules, and basement membranes of proximal convoluted tubules and is in every respect comparable to the material found in the walls of some arterioles showing hyaline arteriolar sclerosis and with tubular casts of inspissated protein. It is believed that the material represents precipitated protein accumulating in spaces created by splitting of the basement membranes of the kidney. The lesion appears to be in every way comparable to arteriolar hyaline sclerosis.

The hyaline-fibrinoid lesion is not strictly specific for diabetes. Its apparent specificity is only quantitative, since the amount of the hyaline-fibrinoid material accumulating in severely damaged diabetic kidneys is greater and its distribution wider than in other renal diseases.

The hyaline-fibrinoid lesions appear to be an important component in the renal lesions associated with diabetes mellitus. It is possible that occurrence of the hyaline-fibrinoid lesion may contribute to renal failure.

444 E. 68th St.

43. Newburger, R. A., and Peters, J. P.: Intercapillary Glomerulosclerosis, Arch. Int. Med. **64**:1252-1264, 1939. Spühler and Zollinger.[9]

VITAMIN A DEFICIENCY IN THE DUCK

Skeletal Growth and the Central Nervous System

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THE NECESSITY of vitamin A for the growth of the skeleton of young ducks was questioned by Fletcher and Rigdon [1] and later categorically denied by Rigdon, Rude, and Bieri [2] and by Rigdon.[3] In each of these three papers a direct and primary effect of vitamin A deficiency upon the nervous system was asserted. The conclusions of these authors—that the duck responds differently to vitamin A deficiency than do the chick [4] and numerous species of mammals [5]—have twofold importance: 1. If they are verifiable, the domestic duck becomes a bird of great interest. 2. If they are not verifiable and not discredited, they create a source of confusion to nutritionists, anatomists, and pathologists.[6]

This study was undertaken for the purpose of ascertaining the effect of a vitamin-A-deficient diet upon endochondral bone growth of young ducks, with particular reference to the axial skeleton and possible results involving the central nervous system.

It is not our intention to describe in detail all the departures from the normal that we found in the vitamin-A-deficient ducks. We will describe our findings,

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From the Division of Nutritional Research, Division of Laboratories and Research, the Children's Hospital; the Department of Nutrition, Harvard School of Public Health, and the Department of Biological Chemistry, Harvard Medical School.

1. Fletcher, D. E., and Rigdon, R. H.: Neurologic Manifestations Associated with Vitamin A Deficiency in Young Ducks: Clinical and Pathologic Study, Arch. Neurol. & Psychiat. **61**:199, 1949.

2. Rigdon, R. H.; Rude, J. C., and Bieri, J. G.: Effect of Hypervitaminosis A and Hypovitaminosis A on the Skeleton of a Duck, A. M. A. Arch. Path. **52**:299, 1951.

3. Rigdon, R. H.: Pathologic Lesions in the Nervous System of the Duck Fed a Ration Deficient in Vitamin A, A. M. A. Arch. Path. **53**:239, 1952.

4. Wolbach, S. B., and Hegsted, D. M.: Vitamin A Deficiency in the Chick: Skeletal Growth and the Central Nervous System, A. M. A. Arch. Path. **54**:13, 1952.

5. (*a*) Wolbach, S. B.: Pathologic Changes Resulting from Vitamin Deficiency, J. A. M. A. **108**:7, 1937. (*b*) Follis, R. H., Jr.: The Pathology of Nutritional Disease, Springfield, Ill., Charles C Thomas, Publisher, 1948. (*c*) Wolbach, S. B.: Vitamin A Deficiency and Excess in Relation to Skeletal Growth, Proc. Inst. Med. Chicago **16**:116, 1946; J. Bone & Joint Surg. **29**:171, 1947.

6. Neurologic Manifestations Associated with Vitamin A Deficiency in Young Ducks, editorial, Nutrition Abst. & Rev. **7**:188, 1949. Wolbach, S. B.: Letter to the Editor, ibid. **7**:319, 1949.

documented with photographs and photomicrographs, which prove that vitamin A deficiency in young ducks results in prompt retardation of endochondral bone

TABLE 1.—*Vitamin-A-Deficient Diet for Duck Experiment*

	Gm./Kg.		Per Kg.
Glucose	523	Thiamine hydrochloride	4 mg.
Casein	180	Riboflavin	8 mg.
Gelatin	80	Pyridoxine hydrochloride	4 mg.
Celluflour*	30	Calcium pantothenate	25 mg.
Corn oil	70	Nicotinic acid	40 mg.
Salts IV†	50	Folic acid	1 mg.
$CaPHO_4$	10	Biotin	200 mcg.
Brewer's yeast	50	Menadione	100 mcg.
Cystine	2	Alpha tocopherol	50 mg.
Choline chloride	5	Vitamin D_3	1,000 I. U.

* Chicago Dietetic Supply Co., Chicago.
† Hegsted, D. M.; Mills, R. C.; Elvehjem, C. A., and Hart, E. B.: J. Biol. Chem. 138:459, 1941.

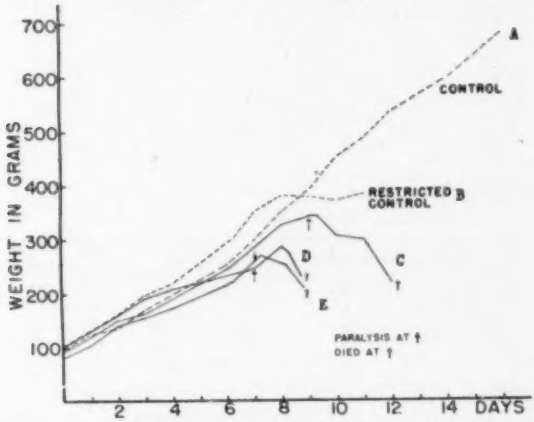

Fig. 1.—Weight graphs of three vitamin-A-deficient ducks, one normal control, and one duck fed a reduced amount of normal diet. The arrows indicate the day on which paralyses were noted and the cross the day of death. These ducks were selected because the photographs and photomicrographs were made from them. *A*, Normal Control Duck 4; *B*, Restricted-Diet Control Duck 2; *C*, Vitamin-A-Deficient Duck 5; *D*, Vitamin-A-Deficient Duck 4; *E*, Vitamin-A-Deficient Duck 2.

growth and therefore a disproportionate growth of the axial skeleton and central nervous system adequate to account wholly for all consequent neurologic manifestations.

EXPERIMENT

Six 3-day-old Pekin ducks were placed on a vitamin-A-deficient diet (Table 1). Five 3-day-old Pekin ducks were placed on the same diet plus an adequate amount of vitamin A acetate.

Pertinent data are shown in the tables. Important facts are that the vitamin-A-deficient ducks became paralyzed sooner than chicks [4] and that in three instances paralysis occurred before the duck had attained maximum weight (Fig. 1). Paralysis was noted first in the other three ducks on the day of maximum weight (Tables 2 and 3).

GROSS PATHOLOGY

All dissections were made after fixation in 10% formalin (formaldehyde 4%) solution of the eviscerated ducks and decalcification in 5% aqueous nitric acid. After decalcification and washing, the ducks were preserved in 10% formalin solution until dissected.

We found it advantageous to inspect the contents of the cranial cavity with dura intact. In the vitamin-A-deficient duck, the longitudinal sinus usually contained little blood, while the lateral sinuses and their tributaries were always engorged, including communicating veins in the parietal and occipital bones and veins of the cerebral hemispheres. In contrast to the chick, there is no anterior confluence of

TABLE 2.—*Vitamin-A-Deficient Ducks*

	Paralyses		Maximum Weight		Death	
No.	Day	Weight, Gm.	Day	Weight, Gm.	Day	Weight, Gm.
1	7	222	8	262	10	180
2	9	258	9	258	9	255
3	10	370	10	370	12	315
4	7	252	9	284	9	284
5	10	344	10	344	13	280
6	9	330	10	330	13	200

TABLE 3.—*Control Ducks, Weight in Grams*

	Food Limited After 5th Day		Food Unlimited		
Day	Duck 1	Duck 2	Duck 3	Duck 4	Duck 5
1	95	100	90	90	100
3	144	150	136	130	150
5	204	212	195	180	214
7	275	304	272	240	306
8	330	348	325	298	384
9	370	380	390	350	460
10	330	333	425	390	520
11	355	370	500	450	600
12	342	370	550	485	640
13	320	335	620	570	750

veins in the duck. In the latter, the veins from the orbits and nose enter separately into the longitudinal sinus and cross the tips of the cerebral hemispheres just posterior to the olfactory bulbs. In vitamin-A-deficient ducks, herniations of the brain could be seen projecting into the longitudinal sinus and into the veins from the orbit and nose (Fig. 2). If the dura was carefully reflected, the herniations remained unseparated from the brain (Fig. 3), a situation not always possible of achievement if the dura and bone are removed together.[7]

Other evidences of compression of the brain were like those found in vitamin-A-deficient chicks,[4] but most conspicuous in the vitamin-A-deficient ducks were dis-

7. In removal of the dura we found no extension between the cerebral lobes or between cerebellum and cerebrum and therefore no obvious falx cerebri or tentorium cerebelli. Both these structures, if they merit the names, are quite delicate and histologically, in sections made through skulls of normal and vitamin-A-deficient ducks, are continuous with the pia arachnoid.

tortion and lateral narrowing of the olfactory bulbs, grooving of the tips of the cerebral hemispheres where crossed by the veins from orbits and nose (Fig. 3), a considerable degree of lateral and posterior overriding of the tecta by the cerebral hemispheres, noticeable anterior molding of the cerebellum between the posterior lobes of the cerebrum, and marked flattening of the flocculi. On the ventral surfaces of the vitamin-A-deficient duck brains the findings were like those described for

Fig. 2.—Vitamin-A-Deficient Duck 3. Paralysis occurred on the 10th day of age, death occurred on the 12th day. The brain with dura intact; enlarged photograph. The arrows point to herniations of the brain which were verified histologically.

the vitamin-A-deficient chick.[4] Frontal-plane sections of three of the vitamin-A-deficient ducks showed in all some degree of herniation of the brain into the foramina of exit of the roots of the fifth nerve and of the eighth nerve.

Examination of the spinal cord in the synsacrum also showed compression effects precisely similar to those described for vitamin-A-deficient chicks (Fig. 4).

MICROSCOPIC PATHOLOGY

The Long Bones.—Endochondral bone growth was studied in the distal end of the femur and proximal end of the tibiotarsus as seen in longitudinal sections through the knee joints. Vitamin-A-Deficient Ducks 1, 2, 5, and 6 (Table 2) and Restricted-Diet Control Duck 2 and Normal Control Duck 4 (Table 3) were used. The controls were killed at 13 days of age.

Fig. 3.—Vitamin-A-Deficient Duck 1. Paralysis occurred on the seventh day and death on the ninth day. The brain with dura removed; enlarged photograph. Note the distortion of the olfactory bulbs, deep grooving of the tips of the cerebral hemispheres, and numerous herniations of the brain, which were carefully dislodged from the veins on stripping off of the dura. Note also the congestion of the veins of the pia. The arrows point to a few herniae cerebri.

We have found endochondral bone growth in normal young ducks to be precisely similar in all details to that in young chicks, which we have studied and recently described.[8]

8. Wolbach, S. B., and Hegsted, D. M.: Endochondral Bone Growth in the Chick, A. M. A. Arch. Path. **54**:1, 1952.

In the vitamin-A-deficient young ducks, possibly because they were studied at an earlier age (9 to 13 days), the over-all appearance at the ends of the bones (distal part of the femur and proximal part of the tibiotarsus) was different from that of vitamin-A-deficient chicks,[5a] although resulting from the same retarded sequences of endochondral bone growth. The difference was visible upon splitting

Fig. 4.—*A*, Restricted-Diet Control Duck 2. Spinal cord exposed; glycogen body in situ; enlarged photograph. The arrow points to an artefact caused by a longitudinal cut of the dorsal column on the right caudad to the glycogen body. *B*, Vitamin-A-Deficient Duck 2. Paralysis and death occurred on the ninth day of age. Glycogen body in situ; enlarged photograph. Note the deep transverse grooving of the spinal cord, cephalad and caudad to the glycogen body, and compression of the latter by the dorsal columns of the spinal cord.

of the decalcified bones preparatory to embedding and consisted of an apparently much deeper metaphyseal zone as compared with the vitamin-A-deficient chick and the normal and restricted-diet duck controls (Figs. 5 and 6).

Fig. 5.—*A*, Vitamin-A-Deficient Duck 5. Paralysis occurred on the 10th day and death on the 13th day of age. Distal end of the femur; × 6.6. Note the absence of a clearly marked boundary between proliferative and growth zones and the long narrow tunnels for blood vessels without evidences of removal of cartilage walls. On the diaphyseal side widening of tunnels and lateral extensions indicate the narrow zone of retarded endochondral bone growth. *B*, Normal Control Duck 4; unrestricted as to food; killed at 13 days of age. Distal end of the femur; × 6.6. Note the sharp delineation of zones of proliferation and growth. Note also that endochondral bone growth has extended epiphysealward, a condition comparable to that of the normal 18-day-old chick illustrated by Figure 1 of a previous paper.[9]

Much of this zone of cartilage, while penetrated by longitudinally directed blood vessels, was not undergoing replacement by bone. The blood vessels for much of their length epiphysealward were not surrounded by fully matured cartilage cells and chondroclasts, and evidences of chondrolysis were absent. In this region these blood vessels, unaccompanied by sequences preparatory to replacement by bone,

Fig. 6.—Restricted-Diet Control Duck 2, killed at 13 days of age. Distal end of the femur; ×7.3. Note the sharp delineation of zones of epiphyseal cartilage and extension of endochondral growth sequences toward the epiphyseal end comparable to the effect of similar conditions in the chick illustrated by Figure 8 of a previous paper.[4]

were like those we have described in the chick [8] as passing through the proliferative zone of the epiphyseal cartilage to enter the cartilaginous epiphysis.

In none of the vitamin-A-deficient ducks studied histologically was there a clearly defined demarcation of zones of proliferation and growth in the distal femoral

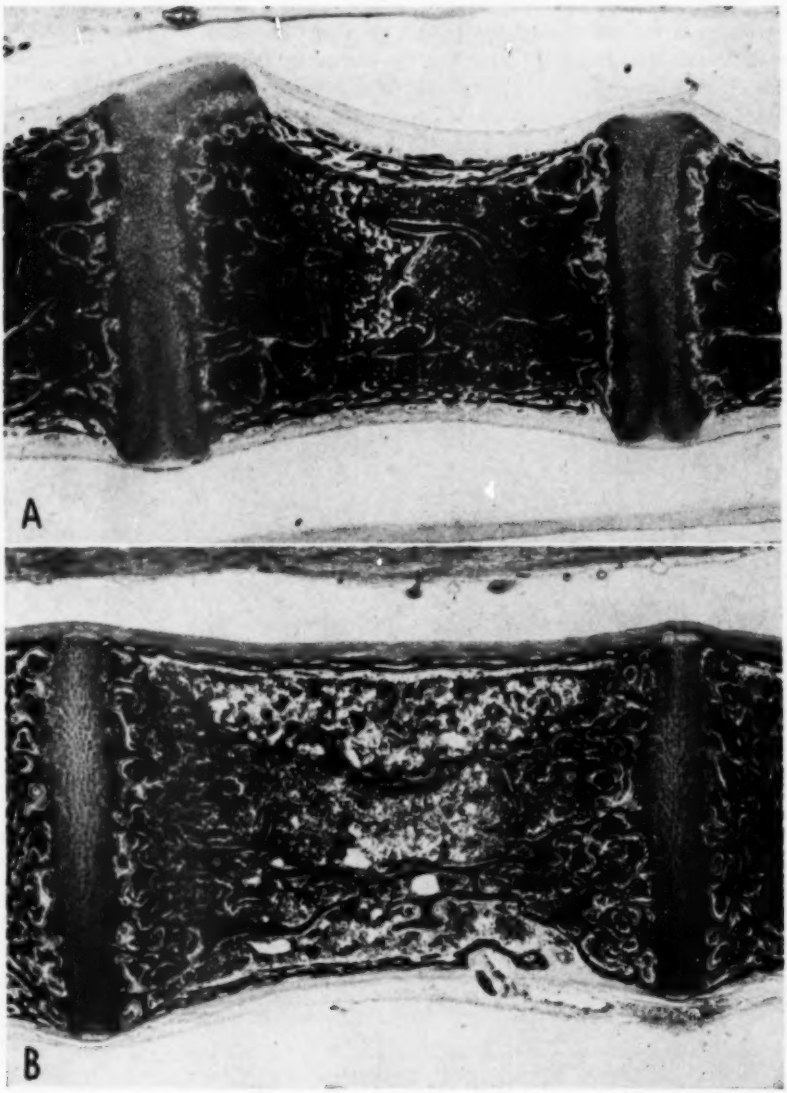

Fig. 7.—*A*, Vitamin-A-Deficient Duck 4. Paralysis occurred on the seventh day and death on the ninth day. Longitudinal sagittal section of the body of a lumbar vertebra; × 37. Endochondral bone growth has ceased. Note the marked concavity of the dorsal side—the result of pressure exerted by the spinal cord. Compare with Figures 7*B* and 8. *B*, Restricted-Diet Control Duck 1, killed at 13 days of age. Longitudinal sagittal section of the body of a lumbar vertebra; × 37. Endochondral bone growth has not entirely ceased. Note the straight line of the cortical bone on the dorsal surface.

epiphyseal cartilage. In Vitamin-A-Deficient Ducks 1 and 6 the proximal tibiotarsal epiphyseal cartilage did show clearly demarcated zones of proliferation and growth. In all the vitamin-A-deficient ducks the proximal tibiotarsal epiphyseal cartilage showed greater activities in endochondral ossification than were found in the distal femoral epiphyseal cartilages, presumably the expression of the greater rate of growth of the tibiotarsus.

The distal femoral epiphyseal cartilages of the normal duck and the restricted-diet control duck showed clearly demarcated zones of proliferation and growth. In both types of controls the zone of growing cells was very narrow as compared with that of the vitamin-A-deficient duck, and lateral resorption of matured cartilage

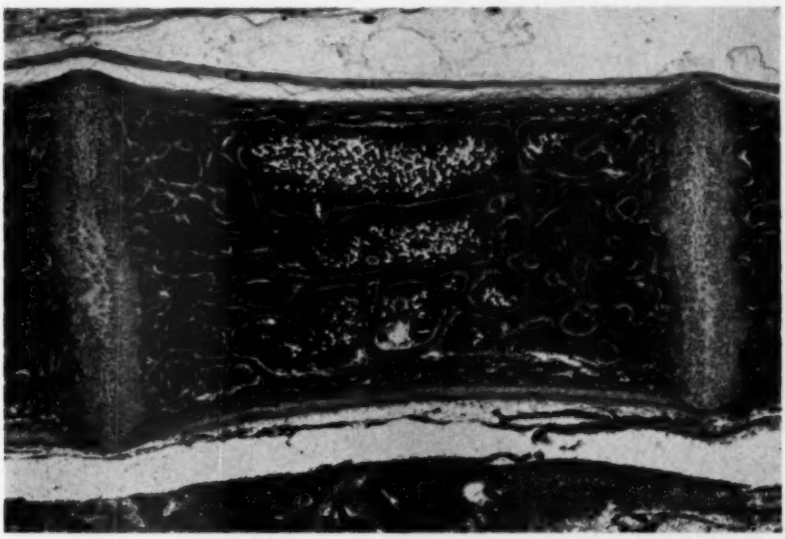

Fig. 8.—Control Duck 4; unrestricted as to food; killed at 13 days of age. Longitudinal section of the body of a lumbar vertebra; × 33.8. Endochondral bone growth is normal. Compare with Figure 7.

cells and the establishment of communications between adjacent canals differed but slightly from corresponding processes in the normal and restricted-diet chick [9] (Figs. 5 *B* and 6).

The outstanding feature of the epiphyseal cartilage of the vitamin-A-deficient duck was the width of the zone of immature cartilage cells, with corresponding absence of bone growth sequences. The zone of matured cells with bone growth sequences in progress was relatively narrow, as was the case with the vitamin-A-deficient chicks. The cytology of the different zones in the duck resembled in all details that described for the chick.[4] The differences between the epiphyseal cartilages of the vitamin-A-deficient ducks and the normal and restricted-diet controls were wholly those resulting from retardation of the sequences necessary for growth of bone—proliferation, growth, and maturation of cartilage cells. The greater width

9. Wolbach and Hegsted.[4, 8]

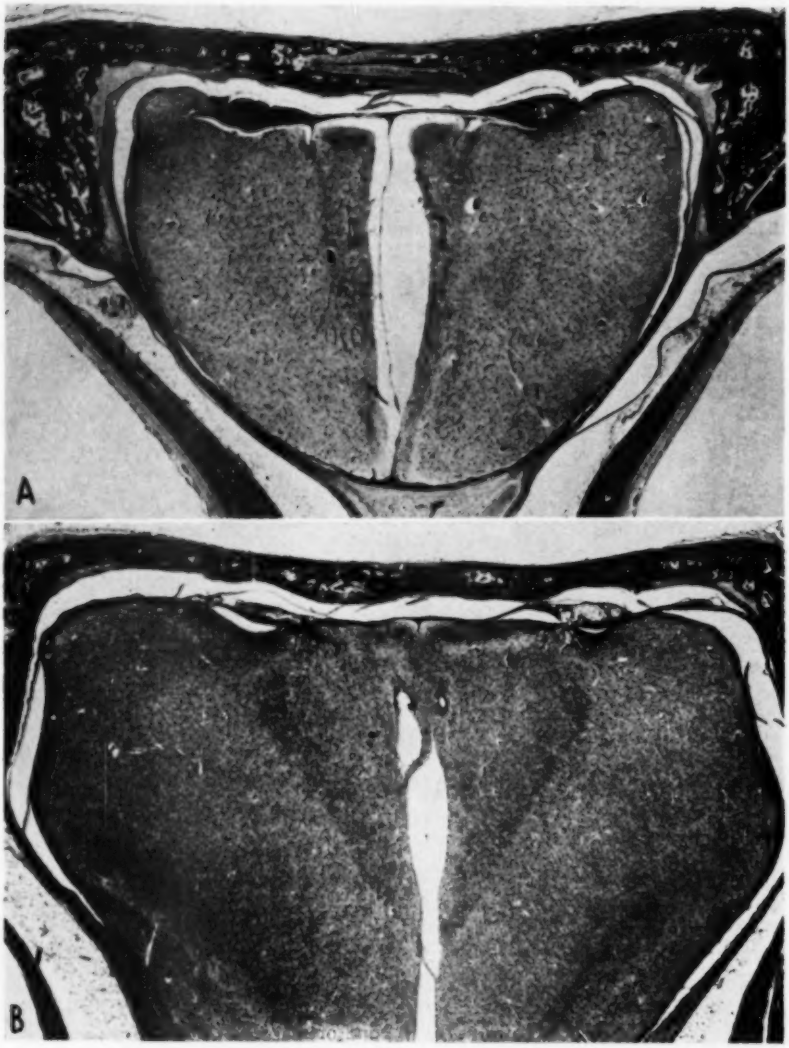

Fig. 9.—*A*, Vitamin-A-Deficient Duck 5. Paralysis occurred on the 10th day of age and death on the 13th day. Frontal-plane section through olfactory bulbs; × 16.6. A relatively large hernia can be seen on the left side and a smaller one on the right. Both project into veins (left from the orbit, right from the nose) filled with blood, which has photographed black. *B*, Vitamin-A-Deficient Duck 4. Paralysis occurred on the seventh day of age and death on the ninth day. Frontal-plane section through the tips of the cerebral hemispheres. Note the herniations on both sides into veins from the orbits.

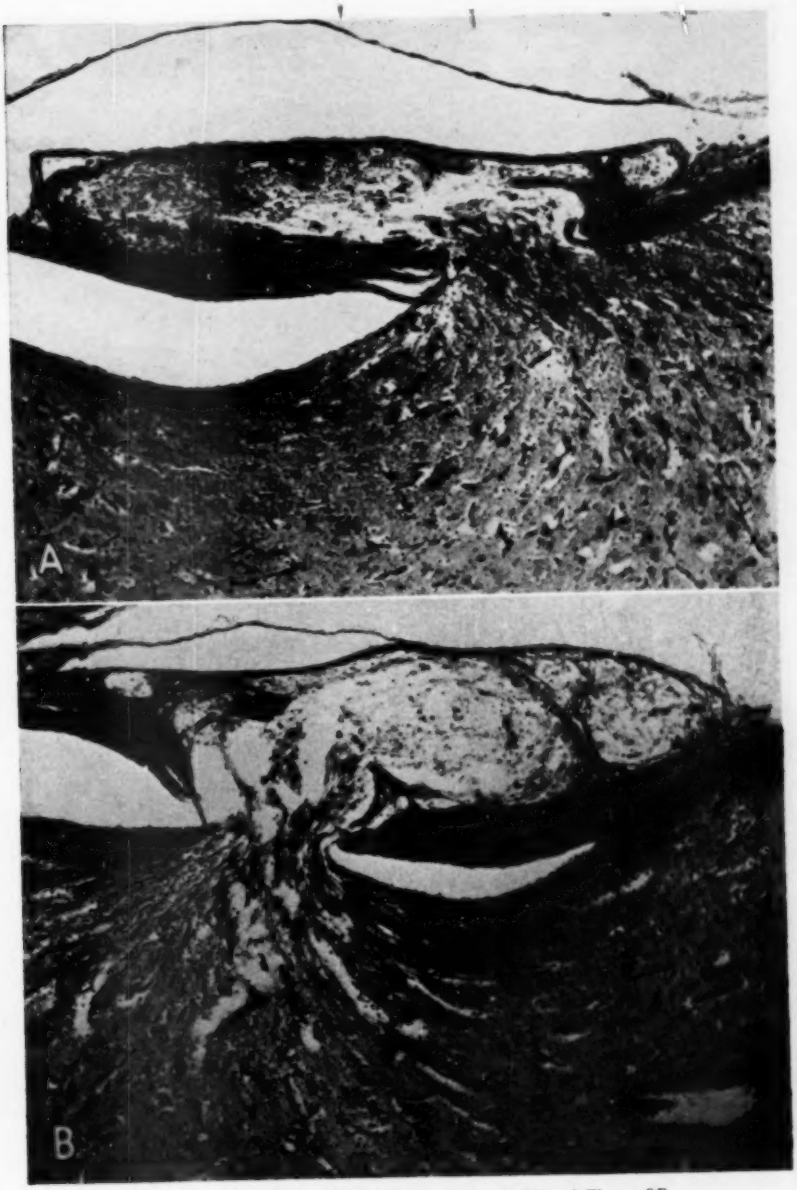

Fig. 10.—Higher-power photomicrographs, × 120, of Figure 9*B*.

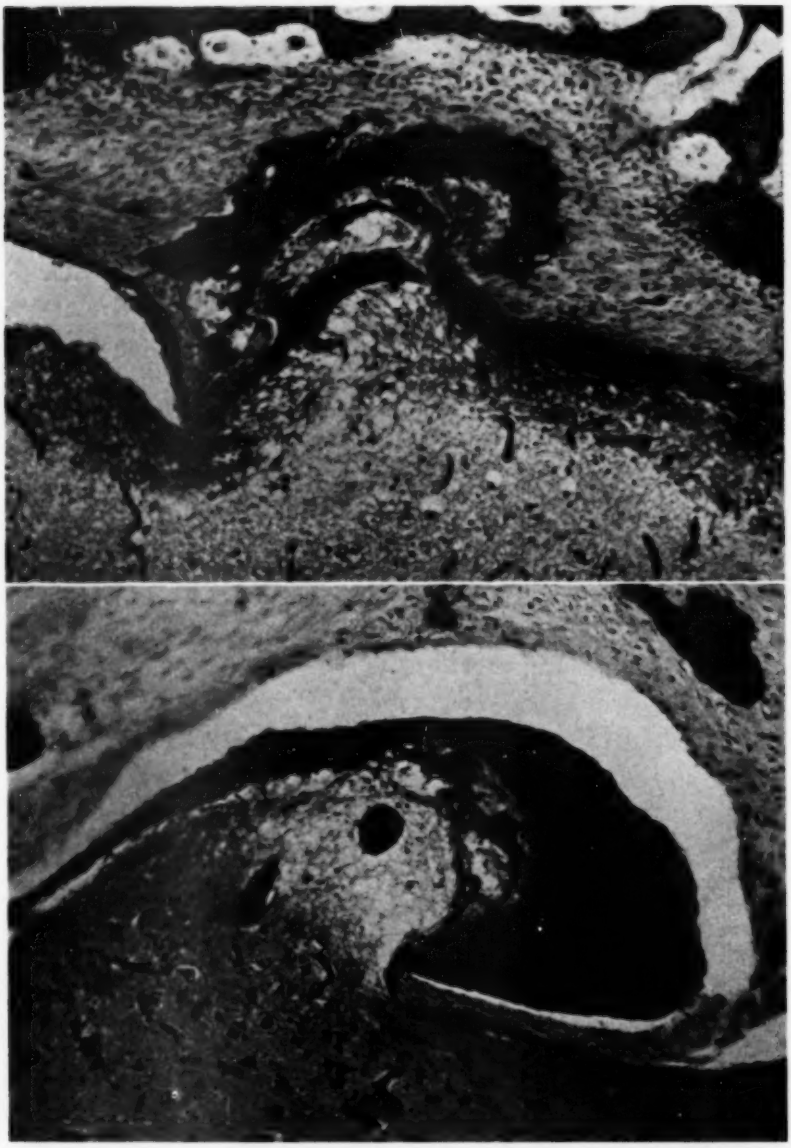

Fig. 11.—Both these photomicrographs at 190 diameters are from Vitamin-A-Deficient Duck 5, from which Figure 9A was made. Both show herniae cerebri into the temperosphenoidal sinuses. From frontal-plane serial sections.

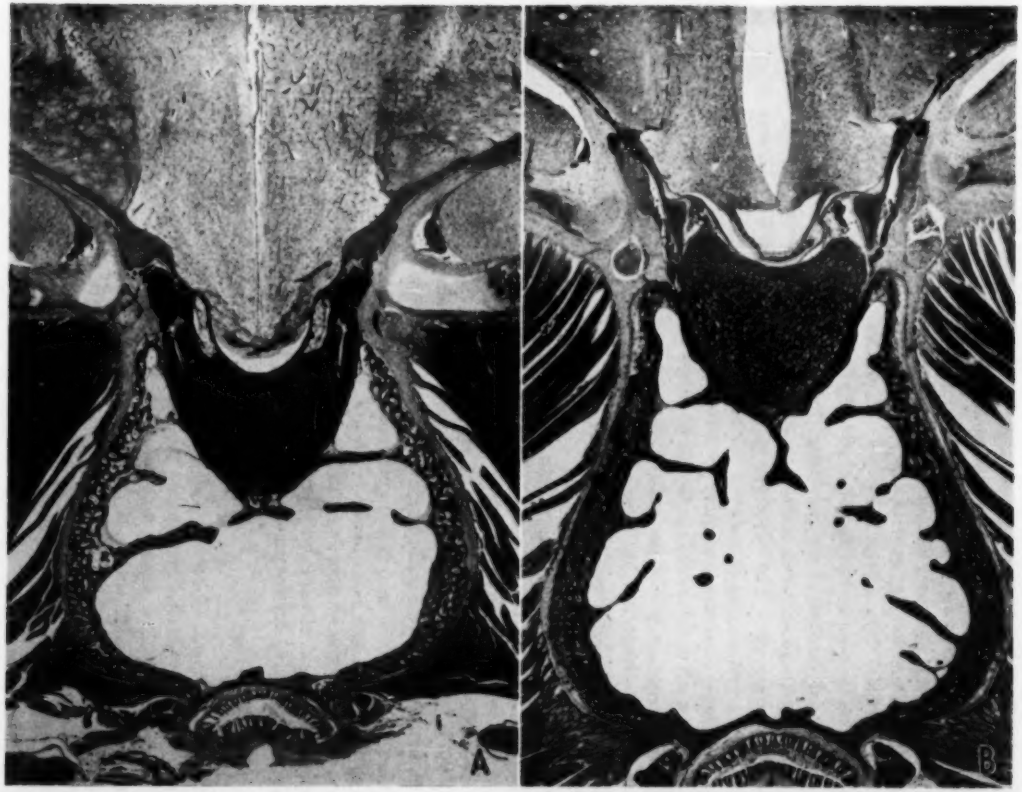

Fig. 12.—*A*, Vitamin-A-Deficient Duck 5. Frontal-plane section, × 16.6, showing compression of the third ventricle and of the infundibulum and downward dislocation into the sella turcica. Note the deep indentation of the anterior lobe of the hypophysis. Note the texture of the sphenoid bone and its pneumatization. *B*, Unrestricted-Diet Control Duck 4. Frontal-plane section, × 16, selected from serial sections for its level corresponding to that in *A*, also one of a set of serial sections. Note the normal third ventricle and infundibulum and the texture of the sphenoid bone.

of the cartilage at the distal end of the femur we believe to be delayed establishment of the epiphyseal cartilage in its completed form. The lack of clearly demarcated zones of proliferation and growth and in one instance (Vitamin-A-Deficient Duck 2) the presence of fetal cartilage in the midshaft of the femur supported this conviction. Another fact of importance is that the ages of the vitamin-A-deficient ducks at death averaged 11 days; those of vitamin-A-deficient chicks we studied,[4] 23 days.

Vertebrae and Bones of the Skull.—Changes in the cancellous bone and cortical bone of the base of the skull were less pronounced than those we described for the chick,[4] but were noticeable, as shown in Figures 7 and 8 for vertebrae and Figure 12 for the sphenoid bone in relation to the sella turcica. The pneumatization of the sphenoid bone apparently had not been affected by the deficiency.

Longitudinal sections of the vertebrae through the synsacrum—lower lumbar and sacral vertebrae—showed marked retardation to complete cessation of endochondral bone growth. The vertebrae of the deficient ducks were shorter than corresponding vertebrae of normal and restricted-diet control ducks, and the bodies of the vertebrae, in contrast to those of the controls, showed less cancellous bone and less dense cortical bone (Figs. 7 and 8).

Frontal-plane sections of the skulls fixed with the brain in situ showed in all regions of endochondral bone formation the same retardation of cartillage cell sequences and bone formation, notably at the junctions of the sphenoid and temporal bones.

The gross findings of herniations into the veins of the nose and orbit on the dorsal and lateral surfaces of the olfactory bulbs were confirmed (Figs. 9 and 10). Also, microscopic herniations into the temperosphenoid sinuses were found. Frequently, tufts of arachnoidal cells were found at the tips of the herniations (Fig. 11), indicating the relationship of arachnoidal villi to multiple herniations of the brain resulting from increased intracranial pressure, as shown for the rat,[10] chick,[4] and human.[11]

Other evidences of increased intracranial pressure were seen in the form of varying degrees of extrusion of the brain into the foramina of exit of the cranial nerves, notably of the roots of the fifth nerve and of the eight nerve. More striking was the compression of the third ventricle, the infundibulum, and stalk of the hypophysis accompanying the forcing of this structure into the sella turcica (Fig. 12).

COMMENT

Because the results of our study of the effects of vitamin A deficiency in young ducks in regard to skeletal growth and the central nervous system are so diametrically opposed to those of Rigdon and associates,[12] we prefer not to discuss or criticize the contents of their papers. Our conclusions entail categorical denials of their statements that the skeletal growth of the duck is not affected by vitamin A deficiency and that the central nervous system lesions necessarily have another origin than that of disproportionate growth of nervous system and bony envelopment.

10. Wolbach, S. B., and Bessey, O. A.: Vitamin A Deficiency and the Nervous System, Arch. Path. **32**:689, 1941.

11. Wolbach, S. B.: Multiple Hernias of the Cerebrum and Cerebellum Due to Intracranial Pressure, J. Med. Res. **19**:153, 1908.

12. Fletcher and Rigdon.[1] Rigdon, Rude, and Bieri.[2] Rigdon.[3]

Allowing for minor anatomical differences, the very rapid growth rate [13] and earlier age of death, the effects of vitamin A deficiency in young ducks upon growth of the axial skeleton and consequent lesions of the central nervous system are identical with those in the chick.[14]

For birds as well as for mammals, vitamin A is as essential for the epiphyseal cartilage cell sequences concerned in endochondral bone growth as it is for vision and for the maintenance of function of many epitheliums. In the duck and chick, as well as in the rat, disastrous results of retarded growth of the axial skeleton appear before growth as a whole is substantially affected.

SUMMARY AND CONCLUSIONS

Vitamin A deficiency in young ducks results in prompt retardation and suppression of epiphyseal cartilage cell sequences concerned in endochondral bone growth. This effect, in common with that in several mammalian species studied [5c] and in chicks, results in a disproportionate growth of the axial skeleton and central nervous system, which continue to grow. The result is compression of the growing central nervous system demonstrable by the occurrence of distortions of brain and spinal cord and multiple herniae cerebri into sinuses and veins of the dura and pia arachnoid at the sites of arachnoidal villi.

13. Hegsted, D. M., and Stare, F. J.: Nutritional Studies with the Duck: I. Purified Rations for the Duck, J. Nutrition **30**:37, 1945.

14. Wolbach and Hegsted.[4] We have found that the administration of excessive amounts of vitamin A to young ducks produces the same acceleration of endochondral bone growth sequences—contrary to the conclusions of Rigdon and associates [2]—described by us for chicks (Wolbach, S. B., and Hegsted, D. M.: Hypervitaminosis A and the Skeleton of Growing Chicks, A. M. A. Arch. Path. **54**:30, 1952). A short paper on the subject is being prepared for publication.

PELIOSIS HEPATIS

Report of Three Cases, with Discussion of Pathogenesis

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PELIOSIS hepatis is a rare condition consisting of diffuse angiomatosis of the liver. The term peliosis hepatis was adopted by Schoenlank.[1] The condition has also been called "telangiectasia hepatis disseminata," [2] "Leberblutung," [3] "multiple Leberblutung," [4] and "angiomatosis hepatis." [5] The cause of peliosis hepatis has not been adequately explained, in spite of the fact that the condition was described, by Wagner, as early as 1861.[6] In a comprehensive review, Zak [7] recently discussed the pathogenesis and summarized the pathologic findings. It is our purpose to report three additional cases and discuss the possible pathogenetic factors.

REPORT OF CASES

Of the three patients reported on, one died in a diabetic coma, one with polyserositis, and the third of pulmonary tuberculosis and rheumatic heart disease. The first two represented the mature stage of peliotic lesions and the third all the stages in the formation of peliotic foci postulated by Senf.[8] For microscopical examination the tissues were stained with hematoxylin and eosin, Wilder's reticulum stain, and Van Gieson's stain.

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Reviewed in the Veterans Administration and published with the approval of the Chief Medical Director. The statements and conclusions published by the authors are the result of their own study and do not necessarily reflect the opinion or policy of the Veterans Administration.

1. Schoenlank, W.: Ein Fall von Peliosis hepatis, Arch. path. Anat. **222**:358-364, 1916.
2. Hedrén, G.: Telangiectasia hepatis disseminata und ihre Pathogenese, Beitr. path. Anat. **45**:306-324, 1909.
3. Mittasch, G.: Über Leberblutungen bei Lungentuberkulose, Arch. path. Anat. **288**:476-482, 1920; Beiträge zur Pathologie der Leberblutungen, ibid. **251**:638-648, 1924.
4. Peltason, F.: Über multiple Leberblutungen bei Miliartuberkolose, Arch. path. Anat. **230**:230-259, 1921.
5. Jaffé, R.: Angiomatosis hepatis beim Menschen, Verhandl. deutsch. path. Gesellsch. **19**:202-214, 1923.
6. Wagner, E.: Fall von Blutcysten der Leber, Arch. Heilk. **2**:369-370, 1861.
7. Zak, F.: Peliosis Hepatis, Am. J. Path. **26**:1-15, 1950.
8. Senf, H. W.: Über die Entstehung der verschiedenen Formen miliarer Leberblutungen (peliosis hepatis), Arch. path. Anat. **304**:539-554, 1939.

CASE 1.—A 35-year-old white man, a tool grinder, known to have had diabetes for eight years, entered the hospital with a severe upper respiratory tract infection associated with considerable coughing and dyspnea. Physical examination at the time of admission revealed an apprehensive, acutely ill patient with Kussmaul breathing, an acetone odor to the breath, and softness of the eyeballs. The heart and lungs were essentially normal. The initial blood sugar level was 363.6 mg. per 100 ml. and the carbon dioxide-combining power 14.5 vol. %. The rectal temperature varied from 97.8 to 102 F. The patient failed to make any clinical improvement in spite of adequate therapy. He passed into a semistuporous state and died in coma.

Autopsy (No. 183-39).—Externally the body showed nothing significant.

Gross Examination: The lungs were voluminous, with edema and areas of bronchopneumonia. Moderate hydrothorax was present bilaterally. The heart was of normal size and shape and showed moderate brown degeneration of the myocardium. The spleen was moderately congested and weighed 145 gm. The kidneys were congested but otherwise appeared normal. The liver weighed 1,965 gm. and measured 28 × 22 × 9 cm. The capsule was smooth, shiny, and a dark brown-purple. Throughout the transparent capsule, numerous blackish-blue dots, varying in size up to 1 mm. in diameter, could be seen. On the cut surface the parenchyma was firm, with obliteration of the liver architecture. The right lobe contained innumerable small, circumscribed, hemorrhagic areas. These measured 1 mm., were slightly depressed from the cut surface, and were brownish-blue. A number of similar areas were scattered throughout the left lobe.

Microscopic Examination: The capsule of the liver showed no thickening or deposits. In the portal areas there was no increase in fibrosis or lymphoid reaction. The portal veins were dilated, intact, and engorged with erythrocytes. Throughout the parenchyma, angiomatous spaces of various sizes were seen; some of these occupied more than a complete high-power field (Fig. 1). The lesions were sharply outlined, delineated only by a thin lining frequently composed of flattened endothelial cells. However, not in all instances could this membrane be visualized or an actual wall be demonstrated. These spaces were either filled with unclotted blood or were thrombosed. Polymorphonuclear cells surrounded some of the lesions. The surrounding liver cord cells were flattened; some were atrophic, with brown pigmentation in their cytoplasm. The central veins were obscured and considerably dilated. The sinusoids about the central veins were moderately dilated and the corresponding cord cells deeply stained. The sublobular veins were moderately dilated, were congested, and occasionally communicated with a mature peliotic lesion.

The red pulp of the spleen was partially obliterated and was congested. Dilated, lake-like capillaries and venules were present.

CASE 2.—A 52-year-old white man, hospitalized for approximately four months, two years prior to admission had had swelling of the abdomen which required paracentesis. Later there was pain in the chest and x-ray examination revealed an opacity in the left chest. He had repeated thoracentesis with withdrawal of clear, pleural fluid. The sedimentation rate was as high as 100. The total protein level was elevated to 8 gm. Because of a questionable mass, laparotomy was performed. The surgeon encountered numerous dense adhesions in the abdomen, and biopsy tissue was found to be inflammatory.

Autopsy (No. 44-49).—The body was well developed but emaciated, weighing 116 lb. (52.6 kg.). The lower extremities showed marked pitting edema.

Gross Examination: The picture was that of diffuse polyserositis. There were adhesive pericarditis, adhesive pleuritis, and a chronic fibrous peritonitis. The spleen weighed 200 gm. It was firm and showed moderate congestion. The liver weighed 1,820 gm. and measured 28 × 20 × 7 cm. The capsule was smooth, shiny, and a deep red-purple. The organ was firm. On section the parenchyma bulged slightly; the cut surface was a homogeneous brownish tan. The entire surface was speckled by 1 mm., slightly depressed, circumscribed, dark-brown areas (Fig. 2).

Microscopic Examination: The sinusoidal spaces were congested. The portal veins were dilated, with intact walls and lumina filled with fluid blood. The liver tissue showed numerous dilated spaces containing blood. Some of the vascular spaces were thrombosed, while others

contained unclotted blood. These angiomatous spaces were lined with intact flattened endothelium, although in some this lining membrane was not readily discernible. The sublobular veins were dilated. Some communicated with the angiomatous spaces. Van Gieson's stain failed to demonstrate fibrous walls about the peliotic areas. The reticulum stain showed some of the thrombi to have a scanty-to-rich fibrillary pattern. In an occasional area there was a sclerotic focus which may have represented the healed stage of a peliotic lesion. The sinusoidal venules were more dilated and congested in the subcapsular areas than elsewhere in the liver parenchyma. The red pulp of the spleen was congested.

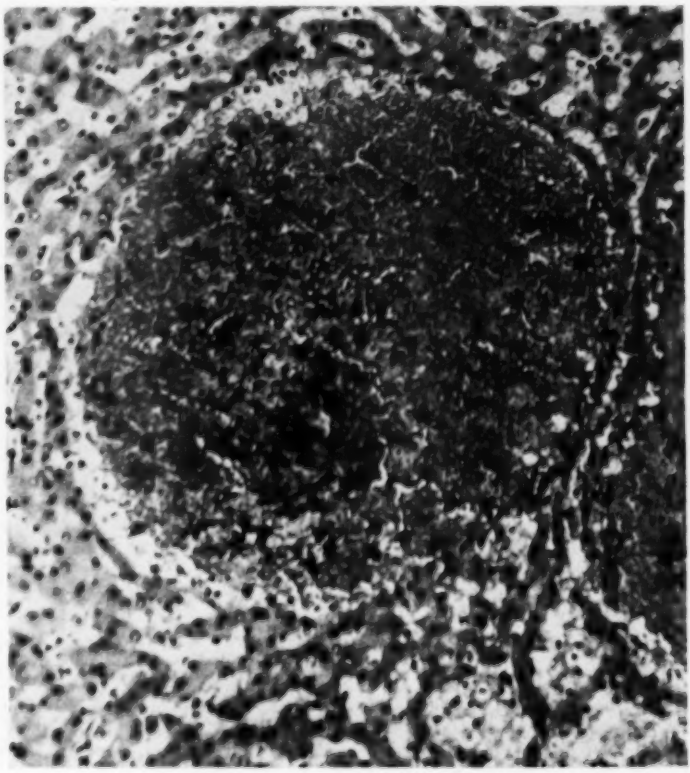

Fig. 1 (Case 1).—Liver, showing angiomatous space containing a recent thrombus, with no distinct endothelial lining; × approximately 200.

Case 3.—A 57-year-old Negro man was hospitalized because of a chest cold with persistent chronic cough, chest pain, and loss of weight of three months' duration. X-ray films revealed far-advanced, active, bilateral pulmonary tuberculosis with cavitation. The physical examination revealed nothing significant. During the last month of his illness, the patient was extremely dyspneic, requiring continuous oxygen administration. Bouts of hiccoughs developed. Both feet showed pitting edema. He became disoriented prior to death.

Autopsy (No. 165-49).—The body was well developed but emaciated, weighing 110 lb. (49.9 kg.). External examination revealed nothing significant.

Gross Examination: The thorax showed dense widespread fibrous pleuritis. The lungs were somewhat contracted and heavy. They revealed fibrocaseous tuberculosis with bilateral cavitation. The heart was small, with pronounced brown degeneration of the myocardium. The mitral and aortic valves were thickened, fibrotic, and distorted, showing evidence of old, healed, rheumatic heart disease.

The internal viscera were congested. The spleen weighed 70 gm. The kidneys were small, weighing 80 and 110 gm., respectively, with arteriosclerotic changes. The liver weighed 1,200 gm. and measured 25 × 15 × 4 cm. The capsule was smooth, shiny and a deep red-purple. The parenchyma was slightly flabby. On cut section, the liver parenchyma bulged slightly and showed considerable congestion, with a suggestion of peliotic foci.

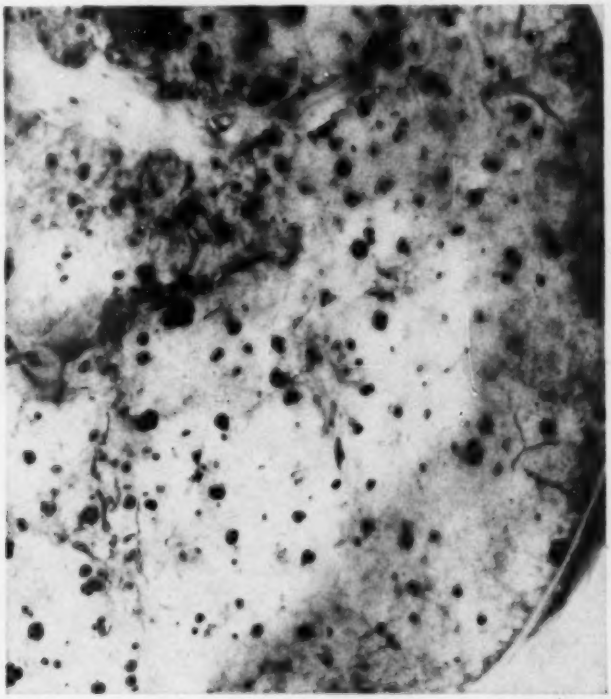

Fig. 2 (Case 2).—Gross view, cut section of the liver fixed in formalin, showing multiple peliotic foci.

Microscopic Examination: The liver was congested. The sinusoidal spaces were widened and engorged with erythrocytes. The adjacent liver cord cells were smaller than normal, and some showed deposits of brown granular pigment. Scattered throughout the parenchyma there were various-sized circumscribed angiomatous areas. Most of these were filled with blood, and their lumina usually were lined with intact endothelium. Others contained fibrin thrombi, some of which completely occluded the lumina. An occasional lumen showed peripheral aggregations of fibrin with central cores of unclotted blood. Various stages of development of those angiomatous spaces could be discerned in the more congested portions of the liver. In the vicinity of the central veins, the sinusoids were extremely congested. The congestion was associated with the formation of intercommunicating vascular lacunae distended with blood (Fig. 3*A*). The extreme congestion had caused atrophy and necrosis of liver cells in some of

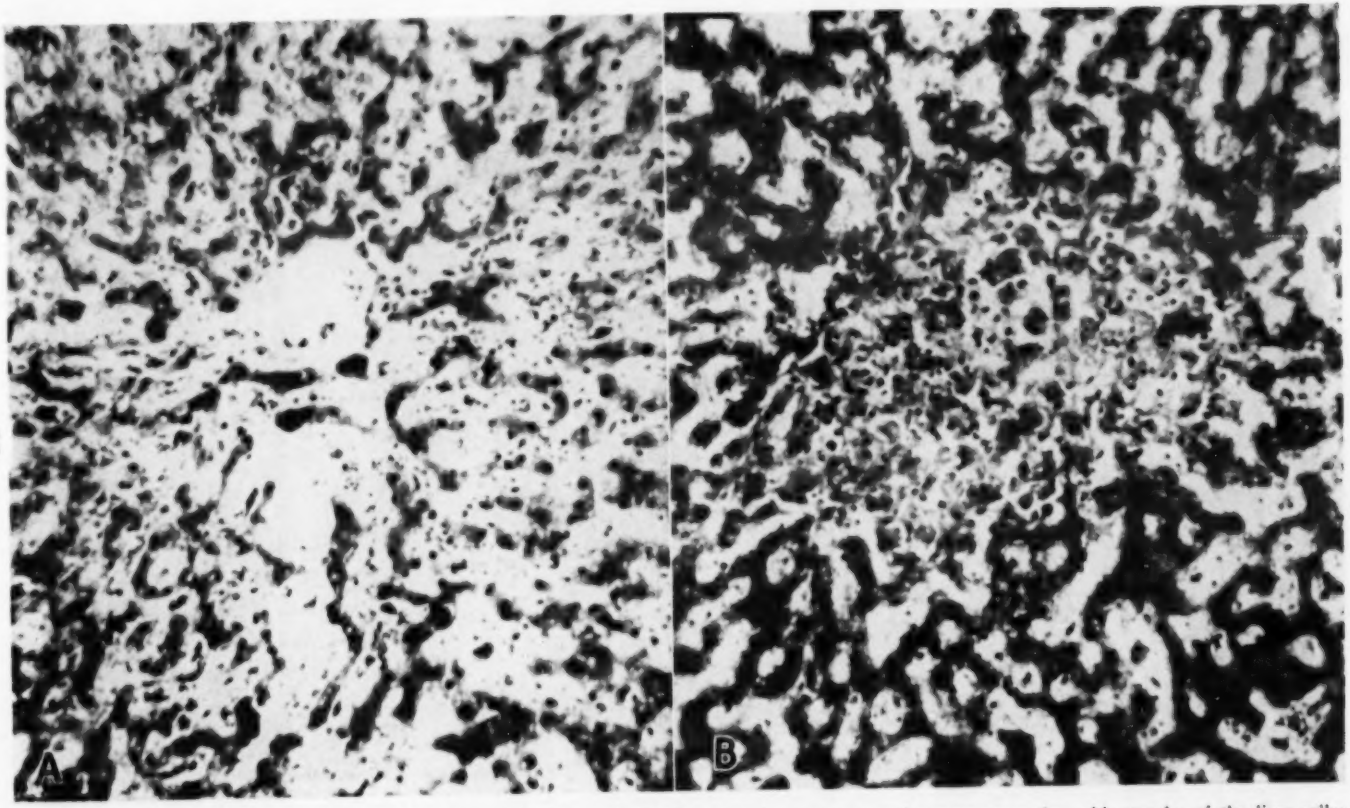

Fig. 3 (Case 3).—*A*, liver in the first stage of formation of a peliotic lesion, showing severe central venous congestion with atrophy of the liver cells; × approximately 200. *B*, liver in an early phase of peliosis, showing a necrotic area with pools of blood; × approximately 200.

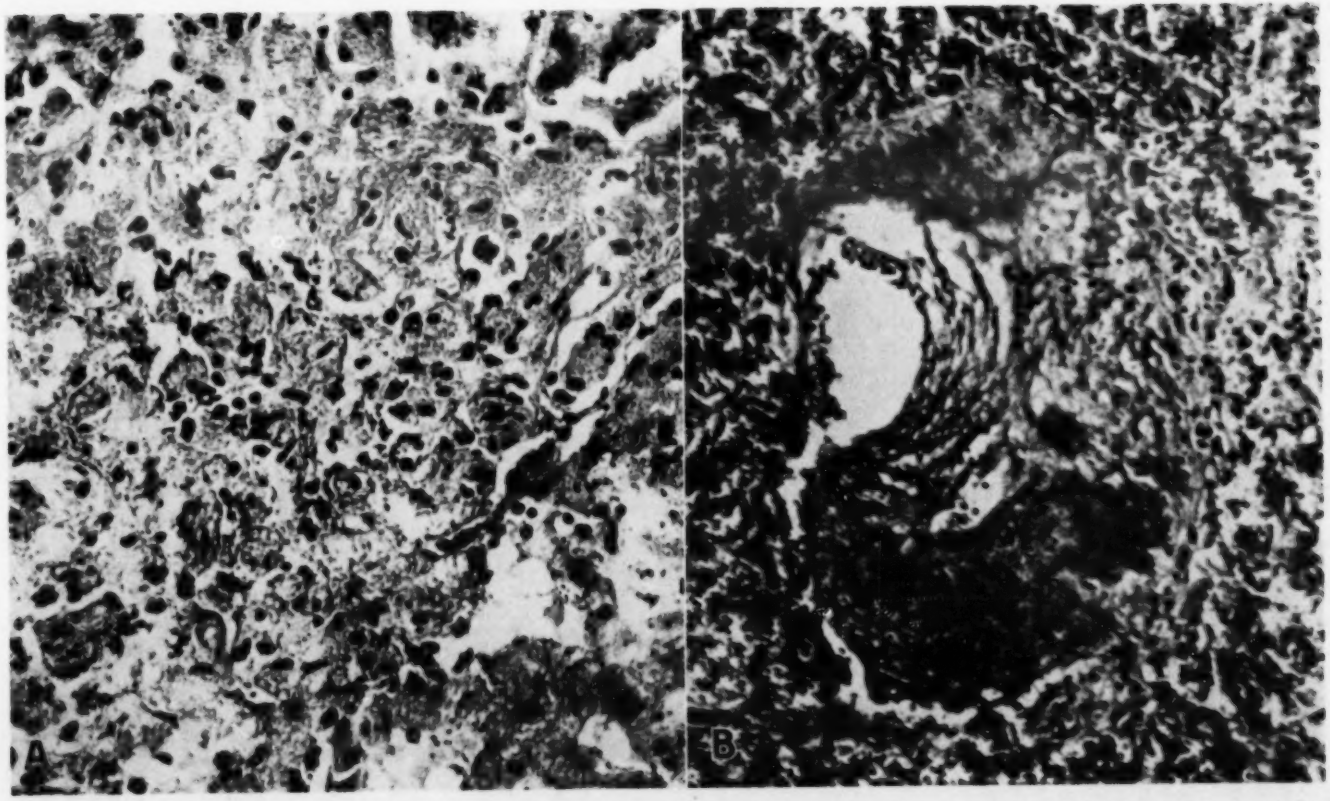

Fig. 4 (Case 3).—*A*, central miliary necrosis of the liver associated with congestion; × approximately 200. *B*, mature phase of peliosis; × approximately 200. After resorption of necrotic tissue and subsequent hemorrhage, a space is formed containing a fibrinous thrombus.

these pools (Fig. 3*B*). In this stage there usually were poorly defined foci heavily engorged with blood and containing fragmented liver cells (Fig. 4*A*). In older and more distinct lesions the liver cells were completely removed and the entire area was filled with fluid blood (Fig. 4*B*). In mature peliotic lesions an endothelial lining had developed. Some of these lesions were either partially or completely filled with fibrin. Not all necrotic foci developed into mature vascular spaces. An occasional lesion was poorly defined, composed of small spaces filled with blood, and partially replaced by delicate collagenous tissue. These areas were attributed to interruption

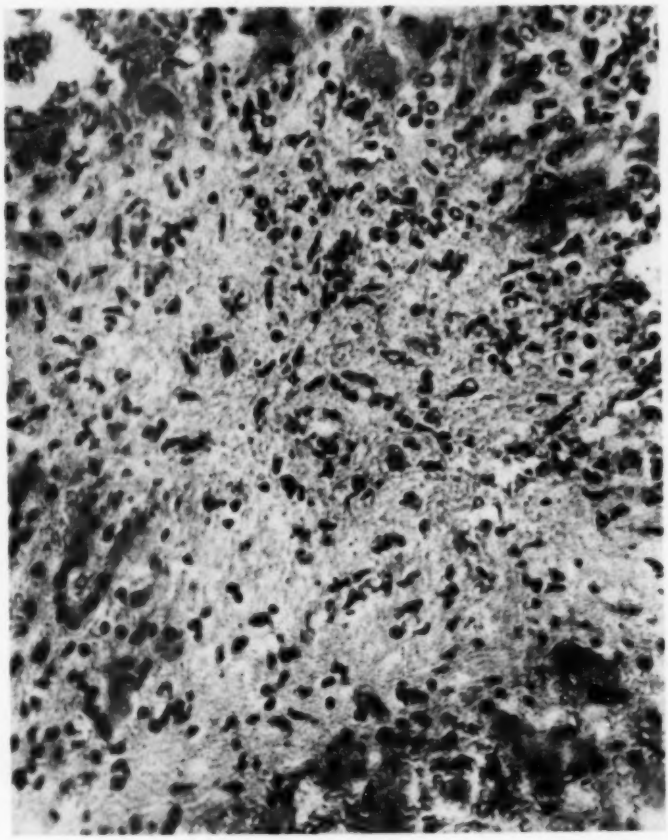

Fig. 5 (Case 3).—Healing of a peliotic focus, showing resorption of a thrombus, with fibrous replacement; × approximately 200.

in the development of mature lesions, with the formation of sclerotic patches (Fig. 5). Such healing lesions were often seen adjacent to mature peliotic foci. The healing lesion lay like a small cap on the larger lesion and was overlaid by a crescentic layer of fibrin within the lumen of the latter. The portal vein, the sublobular vein, and the sinusoidal venules were all dilated and congested. In many areas communications between the sublobular vein and the angiomatous foci were demonstrable.

The sinusoids and venules of the spleen were dilated to form lake-like spaces.

THEORIES OF PATHOGENESIS

Various theories have been offered to explain the occurrence of peliosis hepatis. Although these have been expressed in various ways, they can be classified under three main headings: toxic, congenital, and congestive.

Toxic Theory (Hedrén,[2] Mittasch,[3] Peltason,[4] Zak,[7] Senf,[8] Weber [9]).—The supporters of this theory imply that the formation of miliary necrosis in the liver is due to a toxin. The majority reported cases in which the main disease was pulmonary tuberculosis. Some form of tuberculous toxin was named most frequently. Senf [8] postulated various steps in the production of peliosis hepatis. He believes that an initial miliary necrosis is followed by central or peripheral hemorrhage into the necrotic zones. The bleeding within the liver is supposedly due to increased pressure in the hepatic veins. At this stage, according to Senf, the lesion may progress to a healing phase or continue in its development into angiomatous areas that may or may not be lined with endothelium. Such lesions may be designated the mature phase of peliosis hepatis. These postulated steps were actually observed in one of our cases (Case 3).

Congenital Theory (Jaffé,[5] Cohnheim,[10] Lunghetti,[11] Fabris [12]).—Peliotic lesions of the liver are commonly seen in young cattle.[13] Jaffé and his followers believe the lesions seen in humans are similar to these and that they are congenital.

Congestion Theory (Beneke,[14] Meyer,[15] Strohe,[16] Nissen,[17] Geisler,[18] Pilzer,[19] Schrohe,[20] Grätzer [21]).—The congestion theory has been held by the majority of workers. Gross anatomical studies by the workers listed have revealed some degree of visceral venous congestion, which was usually attributable to the main disease. The congestion theory may also account for the reports of angiomatous lesions of the spleen occurring in 10% of cases.

COMMENT

In Cases 1 and 3 the spleen showed extremely dilated venules and sinusoids. These could readily be attributed to congestion. Very likely, previously reported cases of angiomatosis of the spleen concomitant with peliosis were actually cases of

9. Weber, H. W.: Beiträge zur Morphologie und Pathogenese der Peliosis hepatis, Frankfurt. Ztschr. Path. **59**:52-58, 1947.

10. Cohnheim, J.: Tod durch Berstung von Varicen der Milz, Arch. path. Anat. **37**:413-415, 1866.

11. Lunghetti, H.: Über einen Fall von disseminierter Telangiektasie oder kavernomatöser Entartung der Leber, Zentralbl. allg. Path. **25**:790, 1914.

12. Fabris, A.: Cavernöse Degeneration der Leber, Beitr. path. Anat. **28**:349-362, 1900.

13. Saake, H.: Multiples, disseminirtes Leberangiom des Rindes, Arch. wiss. u. prakt. Thierheilk., Vol. 19, 1894; cited by Fabris.[12]

14. Beneke, R.: Zur Genese der Leberangiome, Arch. path. Anat. **119**:76-80, 1890.

15. Meyer, F. G. A.: Beiträge zur pathologischen Anatomie der Leber, Arch. path. Anat. **194**:212-238, 1908.

16. Strohe, T.: Über die fleckige Kapillarektasie in der Leber der Wiederkäuer, Monatsh. prakt. Thierheilk. **14**:133, 1903.

17. Nissen, A.: Über Phlebektasien der Leber, Beitr. path. Anat. **78**:430-433, 1927.

18. Geisler, W.: Über die sogenannte Peliosis der Leber, Arch. path. Anat. **280**:565-578, 1931.

19. Pilzer, F.: Zur Genese des Angioma cavernosum, Arch. path. Anat. **165**:427-438, 1901.

20. Schrohe, T.: Telangiektasien der Leber, Arch. path. Anat. **156**:37-61, 1899.

21. Grätzer, G.: Über sogenannte "Peliosis hepatis," Frankfurt. Ztschr. Path. **36**:134-145, 1928.

congested, dilated veins. In cases of pulmonary tuberculosis, pulmonary obstruction, cough, and pleuritis with impingement on the inferior vena cava produced increased visceral venous pressure. In the liver the congestion led to peliosis. Although congestion of the liver is found in most cases of peliosis, the cause of the congestion is not always anatomically apparent.

Recent literature has emphasized necrosis caused by tuberculous toxins as the initial phase. However, the majority of authors have implicated congestion as the major cause. It is possible to reconcile these different views by considering that necrosis follows and is the result of severe congestion. Such a sequence is a well-known occurrence in profound passive congestion, such as occurs in far-advanced, right-sided heart failure with the production of central-lobe necrosis. We believe that our Case 3 contains the clue to the explanation of peliosis hepatis. In this case all the stages noted by Senf were seen. As a result of the pulmonary tuberculosis and rheumatic heart disease, the passive congestion of the liver was pronounced, and it was possible to see the actual transition from this congestive state to necrosis and finally peliosis. In Case 1 no reason for the congestion was found anatomically and yet the liver was moderately congested. In Case 2, a case of polyserositis, anatomical features adequately explained the pronounced visceral venous congestion. The patient had adhesive pericarditis, universal adhesive pleuritis, and diffuse chronic adhesive peritonitis, all of which contributed to hepatic congestion.

Our contention differs somewhat from that of Senf, Weber, and Zak. These authors believe that in cases of congestion bleeding into a necrotic focus occurs. Our studies lead us to believe that the necrosis is actually due to the congestion. It might be expected that because of the common occurrence of hepatic congestion the lesion would be found oftener. Undoubtedly peliosis is commoner than published reports would indicate. However, the disorder is obviously rare. There must be another factor, as yet unknown, in addition to congestion to produce the necrosis.

SUMMARY

Three additional cases of peliosis hepatis are reported.

Evidence is presented to support the theory that peliosis follows necrosis of the liver.

In one case it could be demonstrated that the necrosis was associated with severe passive congestion.

ARTERIOSCLEROSIS IN THE DOG

II. Aortic, Cardiac, and Other Vascular Lesions in Thyroidectomized-Hypophysectomized Dogs

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SAN FRANCISCO

THE PRESENT report deals with cardiovascular disease found in dogs subjected to both hypophysectomy and thyroidectomy (HT). This group of HT dogs was selected for study because of the high levels of blood lipides that follow removal of both endocrine glands.[1] The lipemia in these animals is of special interest because it is not produced by the feeding of cholesterol. All dogs in this study were fed a normal diet high in protein and relatively low in fat content.

1. EXPERIMENTAL

Twenty-one adult dogs were used in this investigation. They were fed twice daily, at 8 a. m. and 4 p. m. a diet of lean horse meat and sucrose in amounts recorded in Table 1. Two grams of bone ash was added to each dietary mixture. In addition, each dog received two tablets with its morning meal, one a vitamin mixture[2] and the other a salt mixture.[3] Also added to the morning meal was 3 cc. of sardilene oil.[4]

After a suitable control period, each dog was subjected to complete excision of its pituitary gland; the details of this operation have been described elsewhere.[1] The dogs were next subjected to complete excision of the thyroid gland. In all cases, one or two of the parathyroid glands were preserved with their blood supply intact. All other parathyroid tissue found was transplanted into neighboring muscle.

Aided by grants from the Life Insurance Medical Research Fund and the United States Public Health Service.

Baxter Laboratories, Inc., Research Fellow (Dr. Feinberg); now at the United States Naval Radiological Defense Laboratory, San Francisco (Dr. Entenman).

From the Departments of Pathology (San Francisco) and Physiology (Berkeley) of the University of California School of Medicine and the Department of Experimental Surgery of the Stanford University School of Medicine.

1. Entenman, C.: Chaikoff, I. L., and Reichert, F. L.: Endocrinology **30**:802, 1942.

2. Each vitamin tablet contained: 0.2 mg. of thiamine hydrochloride, 0.2 mg. of riboflavin, 0.2 mg. of pyridoxine, 6.0 mg. of calcium pantothenate, 4.0 mg. of nicotinamide, 50.0 mg. of inositol, 0.2 mg. of folic acid, 6.0 mg. of paraaminobenzoic acid, and 0.01 mg. of biotin.

3. Each salt tablet contained: 600 mg. of NaCl, 450 mg. of magnesium citrate, 200 mg. of KH_2PO_4, 130 mg. of $CaHPO_4 \cdot 2H_2O$, 30 mg. of ferric citrate, 115 mg. of KCl, and 0.1 mg. of KI.

4. Each cubic centimeter of this fish oil contained 400 A.O.A.C. (Association of Official Agricultural Chemists) chick units of vitamin D (equivalent to 300 U.S.P. units) and 1,000 U.S.P. units of vitamin A.

TABLE 1.—*Aortic Disease in Hypophysectomized-Thyroidectomized Dogs**

		Thoracic Aorta							Abdominal Aorta						
		Grossly Visible Plaques			Microscopic Examination				Grossly Visible Plaques			Microscopic Examination			
No.	Supplement Fed	No.	Size	Color	Intimal Thickening	Medial Disease	Lipides†	Cholesterol‡ (Polarized Light)	No.	Size	Color	Intimal Thickening	Medial Disease	Lipides†	Cholesterol‡
HT 8	.....	Intimal wrinkling	.....	.....	0	++	0	0	Not examined	.....	.....	.....	.....	.....	.....
HT 10	.....	0	.....	.....	0	++	0	0	Not examined	.....	.....	.....	.....	.....	.....
HT 18	.....	0	.....	.....	+	+	+	0	Not examined	.....	.....	.....	.....	.....	.....
HT 21	.....	Several	1 mm.	Yellow	0	++	+	0	Not examined	.....	.....	.....	.....	.....	.....
HT 22	.....	1	5 × 10 mm.	Yellow	+	++	+	+	Not examined	.....	.....	.....	.....	.....	.....
HT 47	.....	Intimal wrinkling	.....	.....	+	+	0	0	0	.....	.....	0	+	+	0
HT 49	.....	Intimal wrinkling	.....	.....	0	0	0	0	0	.....	.....	0	0	0	0
HT 34	Pancreas	1	8 mm.	White	+++	0	0	0	0	.....	.....	0	0	0	0
HT 37	Pancreas	0	.....	.....	0	0	0	0	1	1 mm.	White	0	0	0	0
HT 38	Pancreas	1	4 mm.	White	0	+	0	0	0	.....	.....	0	+	0	0
HT 45	Pancreas	1	5 mm.	White	0	+++	0	0	0	.....	.....	+	0	+	0
HT 48	Pancreas	2	4 × 10 mm.	White	+++	++	0	0	1	3 mm.	White	++	0	0	0
HT 50	Pancreas	1	10 mm.	Yellow	0	+	+++	+	0	.....	.....	0	+	++	0
HT 28	Choline	0	.....	.....	+	0	+	0	0	.....	.....	++	0	+	0
HT 29	Choline	Numerous	0.5 × 1 mm.	Yellow	0	++	+++	+++	Several	0.5 mm.	Yellow	++++	++	++++	+++
									Few	0.5 cm.	Gray or White	.....	.....	.....	.....
HT 30	Choline	Several	0.5 mm.	White	+	+	0	0	0	.....	.....	+	+	0	0
HT 31	Choline	0	.....	.....	0	+	+	0	0	.....	.....	+	+	+	0
HT 33	Choline	0	.....	.....	+	++	+	0	Not examined	.....	.....	.....	.....	.....	.....
HT 40	Methionine	Intimal wrinkling	.....	.....	+	+	+	0	Few	1-2 mm.	White	++	0	0	0
HT 41	Methionine	1	5 mm.	White	0	++	0	0	Several	0.5 mm.	White	++	++	+	0
HT 42	Methionine	Intimal wrinkling	.....	.....	+	++	+	0	1; several	3-8 mm. 0.5 mm.	Lt. brown Lt. yellow	++	0	0	0

* 1+, minimal amounts in intima; 2+, moderate amounts in intima; 3+, abundance in intima as well as adjacent media.
† As judged by Sudan IV and Nile-blue stains.
‡ As judged by polarized light and Nile-blue stain.

The exact caloric intake of each dog, recorded in Table 1, was maintained throughout the entire period of observation. Forced feeding was employed when the dogs failed to eat voluntarily.

The completeness of hypophysectomy was established at necropsy. The methods used for the determination of liver and plasma lipides have been previously described.[5]

The dogs were killed by intravenous injection of pentobarbital sodium. The heart, the entire aorta, and the iliac arteries were removed for study. The vascular apparatus was opened longitudinally and its gross appearance noted. After fixation in 10 per cent solution of formaldehyde U.S.P. blocks of tissue were removed from each aorta at the following levels: apex of arch, midthoracic region, and lower abdominal region approximately 2 to 3 cm. above the aortic bifurcation. In a few instances blocks of tissue were removed at other levels, particularly when lesions were grossly visible. Contiguous frozen sections from each block were stained with (1) Sudan IV and hematoxylin and (2) Nile blue. An unstained, frozen section was used for examination with polarized light. These blocks were then embedded in paraffin, and contiguous sections were treated with hematoxylin and eosin stain, Laidlaw's connective-tissue stain, and a combined Verhoeff-Van Gieson stain. Selected sections were also treated with a modified colloidal iron-Prussian blue stain for mucopolysaccharides.

Multiple sections were taken from both ventricular walls and major coronary arteries. When valvular lesions were grossly visible, tissue blocks were also removed from the valves. These cardiac blocks were sectioned and stained in the same manner as were the aortic tissues. Hepatic and renal tissues from the group of dogs fed methionine were treated in a similar fashion.

2. PATHOLOGICAL FINDINGS

The hearts and aortas of 21 HT dogs were excised. Seven of the dogs had been fed the basic diet containing lean meat and sucrose (Table 1). In addition to the basic constituents, six other dogs had received raw pancreas, five had received choline, and three had received methionine. No apparent correlation was observed between the character of the pathological findings and the feeding of any of these supplements.

Gross Description

Heart.—Of the 21 dogs, 5 had lesions of the cardiac valves. In four dogs there were flat, irregular, or streak-like yellow plaques limited to the superior surface of the anterior leaflet of the mitral valve. These varied from 1 to 2 mm. in diameter. In two dogs round yellow plaques measuring 0.5 cm. in diameter were observed in the aortic cusps near the commissures. There were no abnormalities of the pericardial, myocardial, or endocardial layers. Gross evidence of disease of the major coronary arteries was not observed.

Thoracic Aorta.—Of the 21 dogs, 14 had lesions of the thoracic aorta, localized in most instances to the arch. In five animals there was slight intimal thickening and transverse wrinkling of the aortic arch, usually on the convex surface (Fig. 1 *A*). Ten dogs had one or more intimal plaques varying from 1 to 10 mm. and tending to lie in groups. The plaques were usually slightly elevated and in most instances appeared white and fibrous. Their outlines were distinct. They tended to be oval and elongated, although in some instances they had circular outlines.

In one dog there was an inverted, V-shaped, white, fibrous plaque in the midportion of the arch on the concave surface. In another animal thoracic aortic disease was limited to a single yellow, slighly elevated plaque measuring 0.5 × 1 cm. This lay just below the second intercostal arterial openings. One dog showed a cluster of elevated, lemon-yellow intimal plaques on the convex surface in the midportion

5. Kaplan, A., and Chaikoff, I. L.: J. Biol. Chem. **108**:201, 1935. Chaikoff, I. L., and Kaplan, A.: Ibid. **106**:267, 1934.

of the arch. These were somewhat elongated in outline, generally ovoid, and together covered an area measuring approximately 0.5 × 1 cm. The same animal had a slightly elevated, irregular, pale tannish-white plaque in the first portion of the left subclavian artery. In one animal there were several crescent-shaped, bright-yellow plaques that measured 1 mm. in diameter and lay adjacent to the aortic cusps.

Fig. 1.—*A*, thoracic aorta (HT 29) showing intimal wrinkling and scarring in arch; × 2. *B*, abdominal aorta (HT 29) showing multiple nodular fibrous and calcific intimal plaques; × 2.

Abdominal Aorta.—The abdominal aorta was examined in 13 of the 21 dogs, and lesions were found in only 6.

Four dogs had one or more round, slightly elevated plaques, usually lying on the posterior wall in the midportion or lower segment of the abdominal aorta. The plaques varied from 1 to 3 mm. in diameter, were white, appeared fibrous, and usually lay near vascular ostea. The dog with the most extensive thoracic disease also showed pronounced abdominal lesions (Fig. 1 *B*). At the level of the superior mesenteric artery there were several pinpoint, slightly elevated, lemon-yellow plaques. In addition, there were several rounded yellow plaques, each about 1 mm.

in diameter, grouped about the vascular openings in the lower segment of the abdominal aorta. Near and below the level of the mesenteric artery there were larger plaques measuring up to 0.5 cm. in diameter. These were elevated, nodular, pearly-gray or white, and were heavily calcified. Another animal had several round, elevated yellow plaques, measuring 0.5 mm. in diameter, in the lower abdominal segment; on the posterior wall of this segment was an oval, light-brown plaque measuring 3 × 8 mm. Its surface was transversely striated.

Microscopic Description

Cardiac Valves, Endocardium, and Pericardium.—Of the 21 dogs, 7 had microscopic evidence of disease of the mitral or aortic valves. These structures were thickened and consisted of myxomatous fibrous tissue mildly infiltrated with lymphocytes and neutrophilic leucocytes (Fig. 2 *A*). The connective-tissue cells were spindle-shaped. The cells and fibers were usually widely separated. Some cells had distinct vesicular cytoplasm, and delicate reticulum and collagenous fibers lay between these cells. Large amounts of lipide material, demonstrable with Sudan IV, were present in the cytoplasm of the connective-tissue cells and also lay in large, rounded masses in the intercellular spaces. This material stained light pink with Nile blue. In valves having an abundance of lipide material, groups of radially arranged, needle-shaped, refractile crystals were observed with polarized light.

Two dogs in this group showed thickening of the endocardial layer of the left ventricle. In one of them the endocardium consisted of loosely arranged, edematous, fibrous tissue similar to that seen in the altered cardiac valves. Small droplets of lipide material were demonstrated with Sudan IV, and numerous groups of needle-shaped, refractile crystals were observed with polarized light. In the second dog the endocardial fibrous tissue was condensed and partially hyalinized. It contained a few connective-tissue cells. Lipide was not observed in this lesion.

A focus of pericardial hemorrhage associated with lymphocytic infiltration was the only abnormality noted in the pericardial layer of this group of 21 dogs.

Myocardium.—In one dog there was a focal collection of lymphocytes and plasma cells adjacent to the pericardium. In another dog a small focal area of fibrosis containing chronic inflammatory cells was found. In a third dog there was also a small focal collection of lymphocytes and plasma cells associated with early, minimal proliferation of young fibroblasts. A fourth dog showed a larger zone of myocardial fibrosis at the base of the mitral valve. In this fibrotic area, several large calcific deposits were found as well as a small coronary artery with a narrowed lumen (Fig. 2 *B*).

Coronary Arteries.—In 14 of the 21 dogs the coronary arteries were normal. In three dogs the lesions were minimal and usually involved single vessels. In one dog a major coronary artery contained a moderate-sized intimal plaque composed of fibrous tissue which was mildly infiltrated with lymphocytes and plasma cells (Fig. 3 *A*). Although some of the connective-tissue cells appeared vacuolated, lipide material was not demonstrable. In a second dog the wall of a medium-sized coronary artery was thickened as a result of medial hyperplasia (Fig. 3 *B*). Although some of the muscular cells were vacuolated, no lipide substance was present. In a third dog two small coronary arteries showed hyperplastic muscular thickening of their walls, and a few of the cells had vacuolated cytoplasm. The coronary lesions in these three dogs resembled closely those seen in normal dogs.[6]

6. Lindsay, S.; Chaikoff, I. L., and Gilmore, J. W.: A. M. A. Arch. Path. **53**:281, 1952.

Six dogs had lesions involving several coronary arteries. The lesions found in the major coronary arteries and in the smaller, myocardial branches were similar. The earlier lesions resulted from deposition of lipide material in the medial muscular

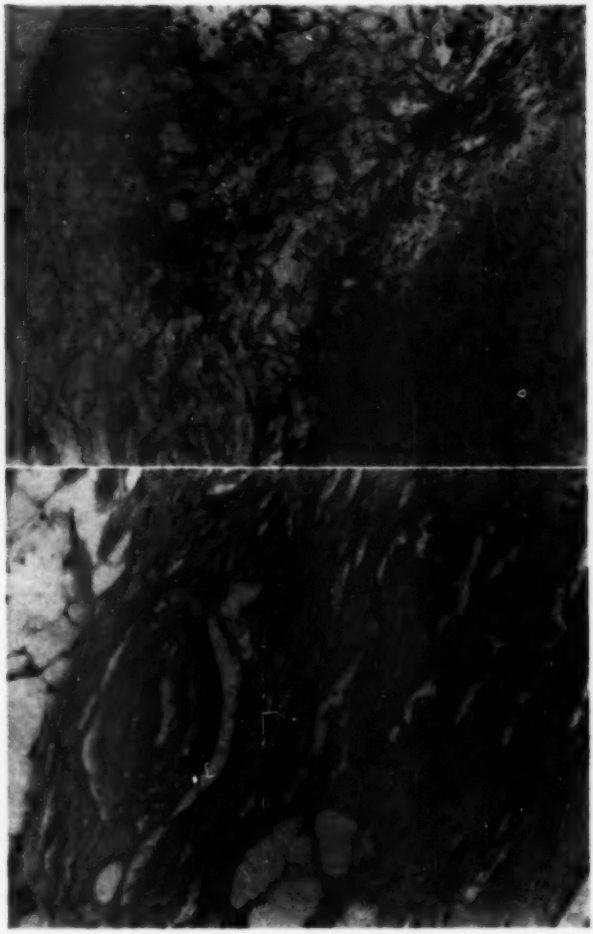

Fig. 2.—*A*, mitral valve (HT 22) showing large lipide deposits and myxomatous fibrosis; × 80; Sudan IV and hematoxylin. *B*, myocardium (HT 37) at base of mitral valve showing thickened small coronary artery and large calcific deposits; × 160; hematoxylin and eosin.

cells as well as in the intimal fibroblasts (Fig. 4 *A*). Associated with increased amounts of lipide deposition was the appearance of numerous groups of foam cells, resulting in intimal thickening and plaque formation (Fig. 4 *B*). These cells were large and possessed vacuolated or finely granular cytoplasm; the nuclei were oval

and usually indented. Each cell was enveloped by delicate reticulum fibers that were associated with the presence of small amounts of fibrillary mucopolysaccharide material. In the vessels showing the greatest amount of lipide infiltration, the lipide-containing foam cells also lay in extruded groups in the media or even in the

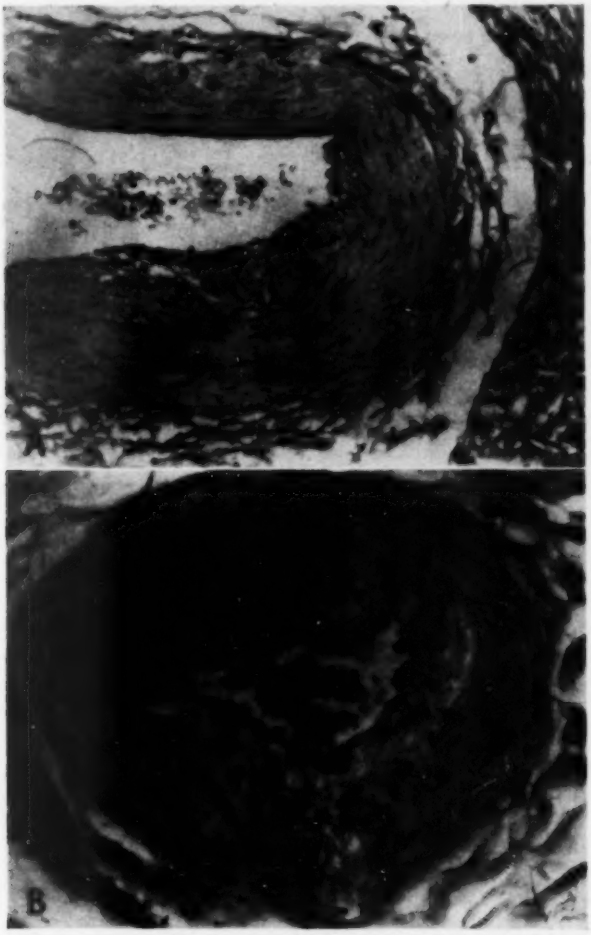

Fig. 3.—*A*, major coronary artery (HT 47) showing fibrous intimal plaque; × 160; hematoxylin and eosin. *B*, medium-sized coronary artery (HT 48) showing medial hyperplasia and narrowing of lumen; × 320; hematoxylin and eosin.

adventitial layers (Fig. 5 *A*). Generally the media was narrowed and compressed. When the masses of foam cells reached the adventitia, there was infiltration of the perivascular tissues with lymphocytes and plasma cells (Fig. 5 *A*). These large collections of intimal foam cells usually destroyed or distorted the internal elastic

membranes. The inner portions of the larger intimal plaques were composed of dense, collagenous fibers, and in these plaques the lipide material in foam cells was found in the deeper portions. The deposits of lipide in the proliferating intimal cells were accompanied first by the appearance of fibrillary mucoid ground substance,

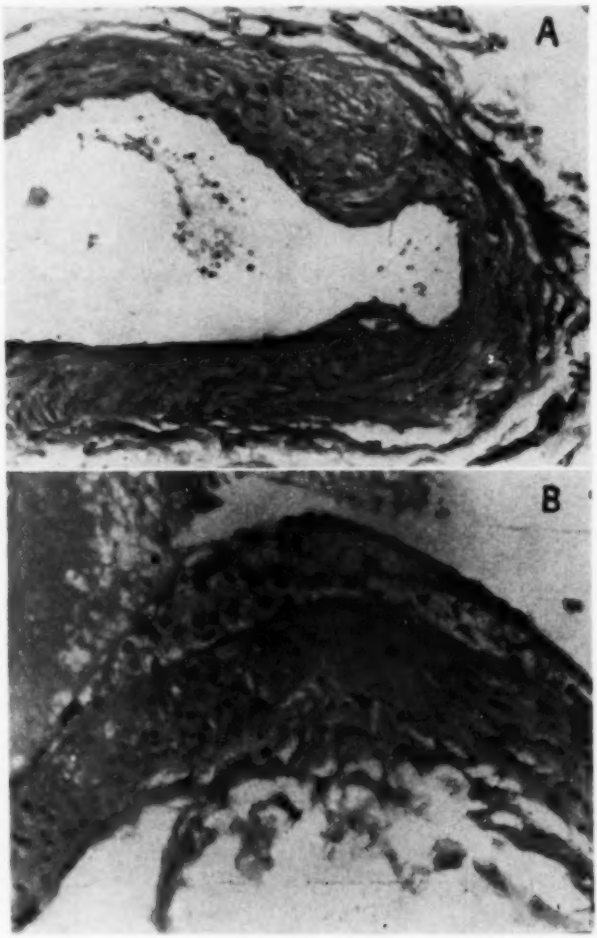

Fig. 4.—*A*, major coronary artery (HT 47) showing vacuolization (lipide) of intimal and medial layers; × 160; hematoxylin and eosin. *B*, major coronary artery (HT 40) showing small intimal plaque composed of foam cells; × 320; hematoxylin and eosin.

which was eventually replaced by reticulum and collagen fibers. In some arteries, the collections of foam cells were limited to the medial layer. In many vessels the intimal foam cells were so numerous that they partially or completely occluded the vascular lumens (Fig. 5 *B* and *C*). Sudan IV stain showed that most of the lipide

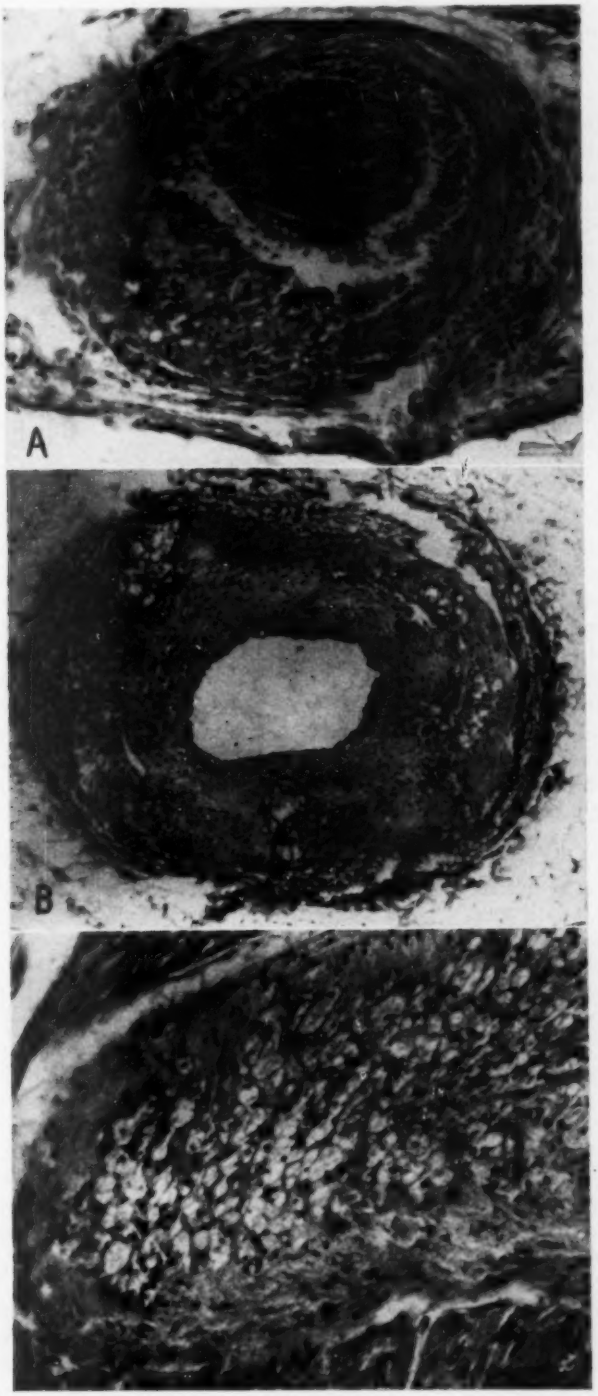

Fig. 5.—*A*, coronary artery (HT 42) showing foam cells in all lavers of the vessel; × 160; hematoxylin and eosin. *B*, coronary artery (HT 41) showing extensive infiltration of vascular layers with foam cells and fibrous tissue; × 80; hematoxylin and eosin. *C*, coronary artery (HT 42) showing obliteration of lumen by intimal foam cells; × 160; hematoxylin and eosin.

material lay in the cytoplasm of the macrophages or foam cells; however, considerable amounts of lipide material were also present in the intercellular substance and in the cytoplasm of the medial muscular cells. The lipide stained a light pink with Nile blue. Even in vessels containing an abundance of lipide substance, very little refractile material was demonstrable with polarized light. When present, it appeared as small groups of needle-shaped, refractile crystals.

Aorta.—General Characteristics: Of the 21 dogs, 14 had microscopic evidence of intimal disease of either the thoracic or the abdominal aorta or of both. Intimal lesions were found by microscopic study in four dogs that showed no gross evidences of aortic disease. The intimal lesions in the thoracic and abdominal segments were similar, although the medial structures of the two aortic segments differ—muscular elements being more abundant and elastic fibers fewer in the media of the abdominal aorta. Lesions of the medial layer were observed in 17 of the 21 dogs, and these were more frequent in the thoracic than in the abdominal portion.

Intima: 1. General appearance. The earliest evidence of disease of the intima was usually an alteration of the internal elastic membrane. This consisted of fraying or splitting, often associated with distinct reduplication. In many sections fragmentation or even loss of the internal elastic membrane was observed even in the absence of other demonstrable intimal alteration. The earliest intimal thickening was the result of deposition of amorphous or fibrillary mucopolysaccharide material adjacent to the fragmented internal elastic membrane (Fig. 6*A*). The smaller intimal plaques consisted entirely of this material. Enlargement of intimal plaques resulted from progressive deposition of mucoid substance and replacement by collagenous fibers. In vessels showing multiple large plaques, the intima between them was generally slightly or moderately thickened. The fibrous tissue comprising the plaques varied in appearance. The smaller plaques or early lesions of intimal thickening were usually composed of loosely arranged fibroblastic cells and fibers. Frequently, particularly in the larger plaques, the cells and fibers were oriented in a perpendicular or circumferential manner (Fig. 6*B*). The looseness of the cellular and fibrillar arrangement was more pronounced in frozen than in paraffin sections. In a few early intimal plaques, the fibroblastic cells were immature; their nuclei were hyperchromatic. In many instances, there was pronounced vacuolization of the intimal fibroblasts.

There was usually lamination of the larger plaques (Fig. 7*A*). The older, deeper portions were more compact, the intercellular fibrils were coarser, and their fibrocytes appeared inactive. The inner portions of these plaques consisted of less mature cells and fibers. Multiple layering of these plaques was observed in only one dog. Several of the larger plaques in another dog were characterized by a basophilic nonfibrillary stroma which separated enlarged, rounded connective-tissue cells. The tissue of these plaques closely resembled cartilage (Fig. 7*B*).

Intima: 2. Elastic and connective tissues. The Verhoeff-Van Gieson stain revealed most distinctly pronounced alterations of the elastic tissue of the intimal layer. The internal elastic membrane occasionally showed fraying, splitting, or fragmentation even in the absence of intimal thickening. The amounts of elastic tissue in the plaques varied directly with their size.

The small plaques contained only a few delicate, wavy, elastic fibers, usually lying transversely. Elastic fibers were usually absent in the inner portions of larger intimal plaques, but were present in the deeper portions. They were most

abundant in the deepest segments adjacent to the media, tended to be laminated or wavy, and were often as coarse as the underlying, adjacent, internal elastic membrane (Fig. 8*A*). The finer elastic-tissue fibrils in the earlier plaques were intimately associated with the cytoplasm of the fibroblasts. In rare instances elastic

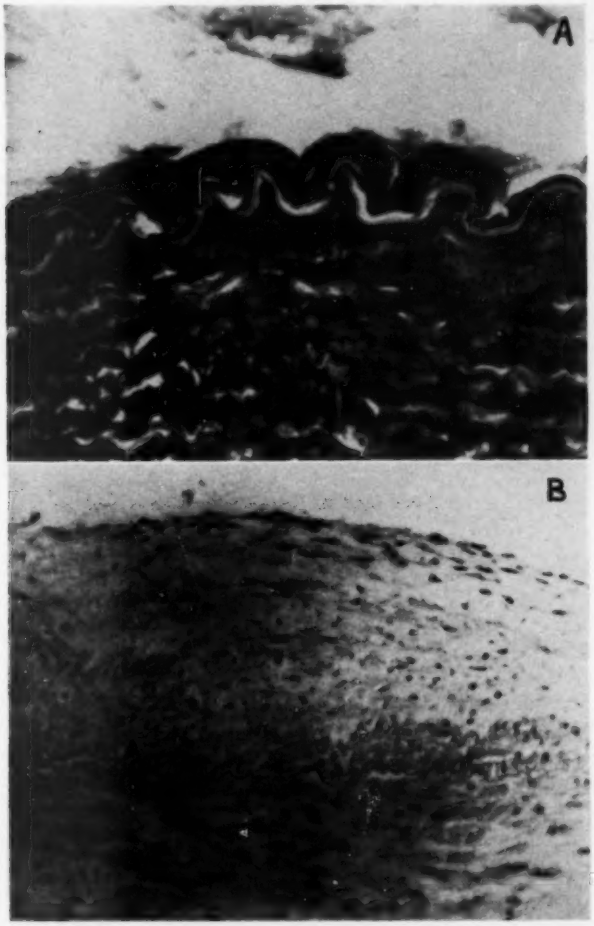

Fig. 6.—*A*, abdominal aorta (HT 34) showing fragmentation of internal elastic membrane associated with intimal deposit of mucopolysaccharide; × 320; colloidal iron-Prussian blue. *B*, abdominal aorta (HT 42) showing circumferential arrangement of connective-tissue cells and fibers of plaque and reduplication of internal elastic membrane; × 160; hematoxylin and eosin.

fibers were wider and more numerous in the superficial layers of the plaques. In some plaques the thicker, coarser elastic fibers were degenerating and had a fragmented or granular appearance. The cartilaginous intimal plaques did not contain elastic fibers.

The Laidlaw connective-tissue stain revealed delicate reticulum or coarse, wavy, collagenous fibers closely associated with the cytoplasm of the fibroblasts in the plaques.

Intima: 3. Lipide material. Lipide material was found in the wall of the aorta in 12 of the 21 dogs. In one animal the only infiltration consisted of small sudano-

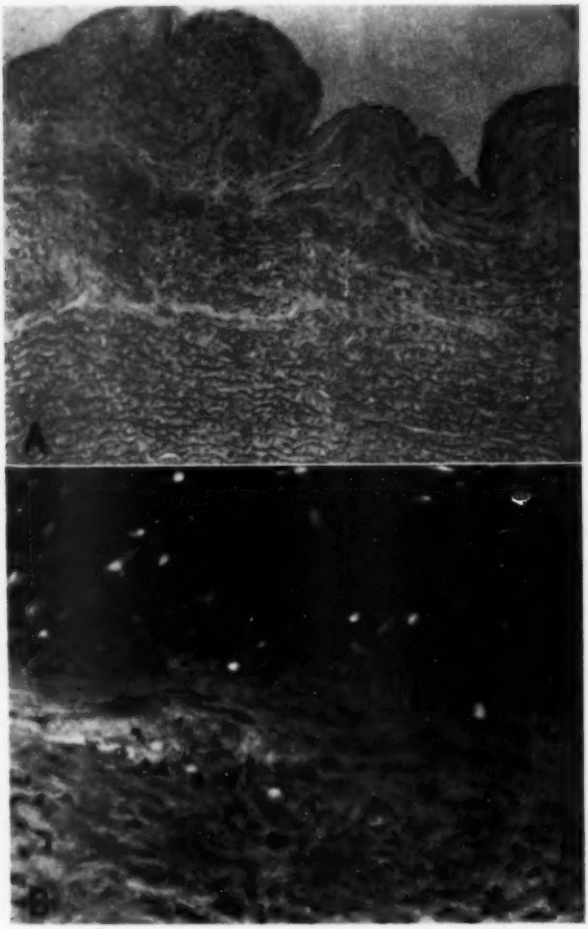

Fig. 7.—*A*, thoracic aorta (HT 48) showing lamination of larger intimal plaque; × 80; hematoxylin and eosin. *B*, abdominal aorta (HT 29) showing cartilaginous metaplasia of intimal plaque; × 160; hematoxylin and eosin.

philic droplets in the cytoplasm of the intimal endothelial cells. Larger amounts of lipide were observed in the thickened intima, or in intimal plaques, in the majority of animals (Fig. 8 *B*). These appeared as droplets in the cytoplasm of the intimal fibroblasts as well as in the extracellular spaces. Groups of macrophages filled with

fat were found in only a few instances. These were limited to the largest plaques containing abundant lipide. In the cartilaginous intimal lesions, lipide material was present only in the adjacent fibrous portions, much of it in macrophages.

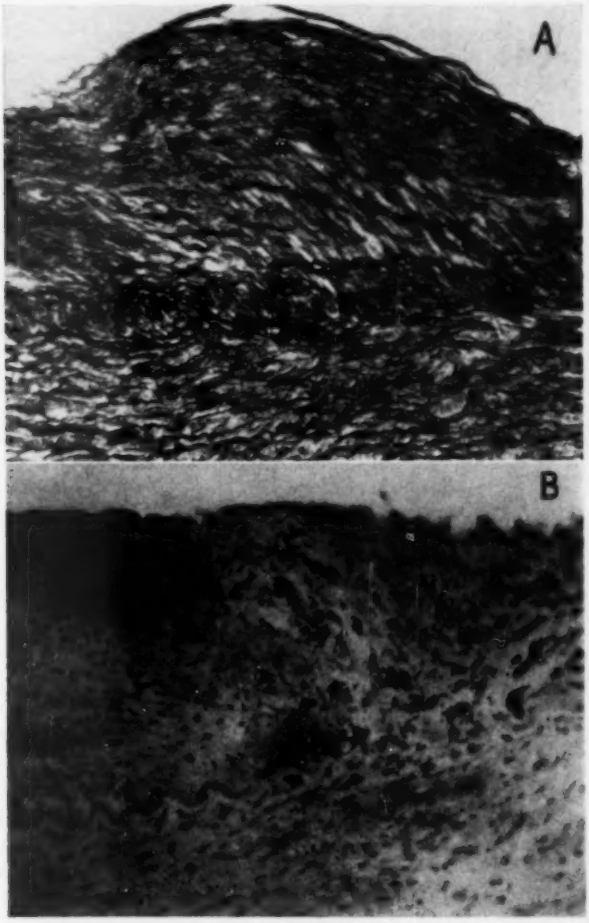

Fig. 8.—*A*, thoracic aorta (HT 48) showing abundance of elastic fibers in intimal plaque; Verhoeff-Van Gieson. *B*, thoracic aorta (HT 29) showing lipide deposits in intimal plaque and adjacent media; × 160; Sudan IV and hematoxylin.

When only a small amount of lipide was found, it was deposited near the internal elastic membrane. When more abundant, it was concentrated in the deeper portions of the intimal plaques. This material stained much less distinctly with Nile blue and varied from pink to pale violet. In only three animals was refractile material observed with polarized light in the intimal or medial layers.

Intima: 4. Mucopolysaccharides. Certain selected sections of the aorta were studied after being stained for acid mucopolysaccharides by the iron-Prussian blue method. The thickened intima and intimal plaques contained an abundance of blue-staining material, presumably mucopolysaccharide. Usually the material was fibrillar and intimately surrounded the connective-tissue cells of the plaques. In some instances the material appeared amorphous or even granular. The smaller plaques consisted entirely of this material. One of the earliest lesions observed consisted of a thin layer of fibrillary mucopolysaccharide enveloping a fragmented, degenerating segment of the intima (Fig. 6*A*).

In the larger plaques the deeper layers generally contained delicate, wavy, collagenous fibers arranged transversely. These appeared to be replacing the fibrillary mucoid ground substance.

Media: Lesions of the medial layer were observed in 17 of the 21 dogs and were more frequent in the thoracic segment than in the abdominal portion of the aorta. The medial alteration included focal edema which separated muscular and elastic fibers. The edema appeared often to have been followed by deposition of collagen.

In the aortic media of some dogs, there were irregular groups of smooth muscular cells which appeared hyperplastic. Where edema was present or where focal collections of fibroblasts or muscular cells were grouped, the elastic tissue was fragmented or absent. The remaining elastic fibers surrounding these foci were coarse and appeared condensed. The focal lesions were also characterized by pronounced vacuolization of the cytoplasm of muscular cells and fibroblasts. These alterations of the medial layer were identical with those in normal dogs, described previously.[6]

In 4 dogs showing wrinkling of the aortic intima of the arch, no intimal thickening was observed on microscopic examination. However, the intima and inner media had deep indentations, and in these areas there were considerable coarsening, reduplication, and condensation of the inner medial elastic tissue (Fig. 9*A*).

In the majority of HT dogs, the medial layer contained variable amounts of lipide material. When this substance was most abundant in the thickened intima, large amounts were usually observed in the adjacent media as well. In most instances, lipide droplets were observed in the cytoplasm of connective-tissue and muscular cells, but occasionally they appeared in intercellular spaces as well. They were particularly plentiful in the vacuolated medial cells.

In nine dogs lipide material appeared only in the media of the thoracic or abdominal aorta (Fig. 9*B*). In these animals intimal disease was not present. When only minimal amounts were demonstrated, they tended to be deposited along the internal elastic membrane. When more lipide was present, it was found mainly in vacuolated connective-tissue cells. Collections of lipide-filled macrophages were not found in the aortic media. When medial lipide material was abundant, it stained pale pink with Nile blue.

Small amounts of refractile material were visible with polarized light in those few instances in which large amounts of lipide were present. They appeared as small, scattered, needle-shaped, delicate crystals.

The medial layer contained variable amounts of mucopolysaccharide, which was usually more abundant in the inner portion of the vascular wall. While some of this material appeared to be intracellular, involving both muscular and fibrous cells, most of it was extracellular and lay between and on the surfaces of elastic lamellae.

There was, as a rule, more mucoid material in areas where elastic tissue was deficient and where collagenous deposits had appeared. In some instances the mucoid material appeared to be undergoing replacement by collagenous fibers.

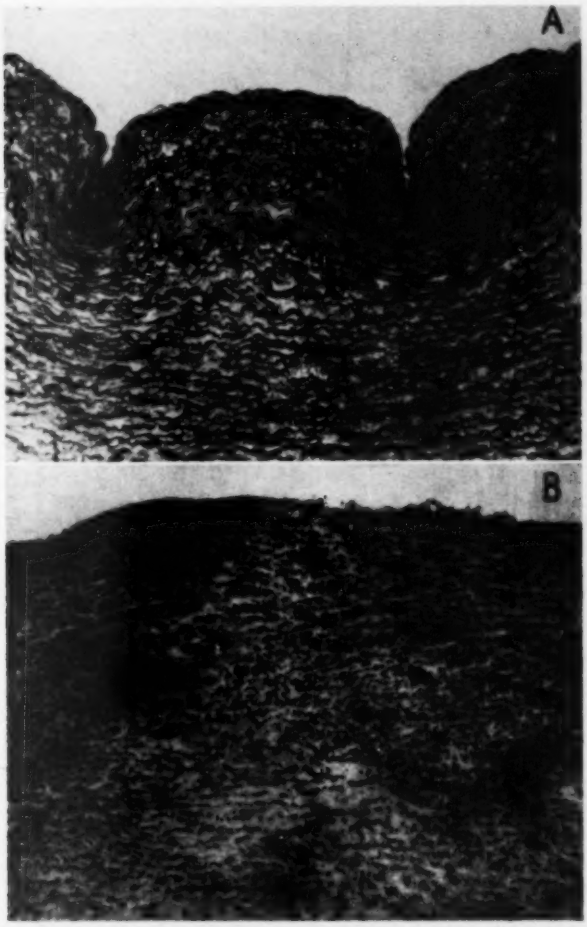

Fig. 9.—*A*, thoracic aorta (HT 40) showing medial indentation and coarsening of medial elastic fibers; × 160; Verhoeff-Van Gieson. *B*, abdominal aorta (HT 29) showing lipide deposits in media; × 160; Sudan IV and hematoxylin.

Duplicate paraffin sections of the aortas of some animals were treated with testicular hyaluronidase and then stained by the iron-Prussian blue method. The intimal mucoid substance was partially removed by treatment with the enzyme. However, very little of the medial mucopolysaccharide was recovered by this treatment.

Muscular Arteries (Renal, Hepatic, and Other Aortic Branches).—In three animals one or more large branches of the abdominal aorta had pronounced arteriosclerotic lesions. Three dogs had lesions in one or more of the large renal arteries (Fig. 10*A*), and one had severe arteriosclerosis of a hepatic arterial branch. In

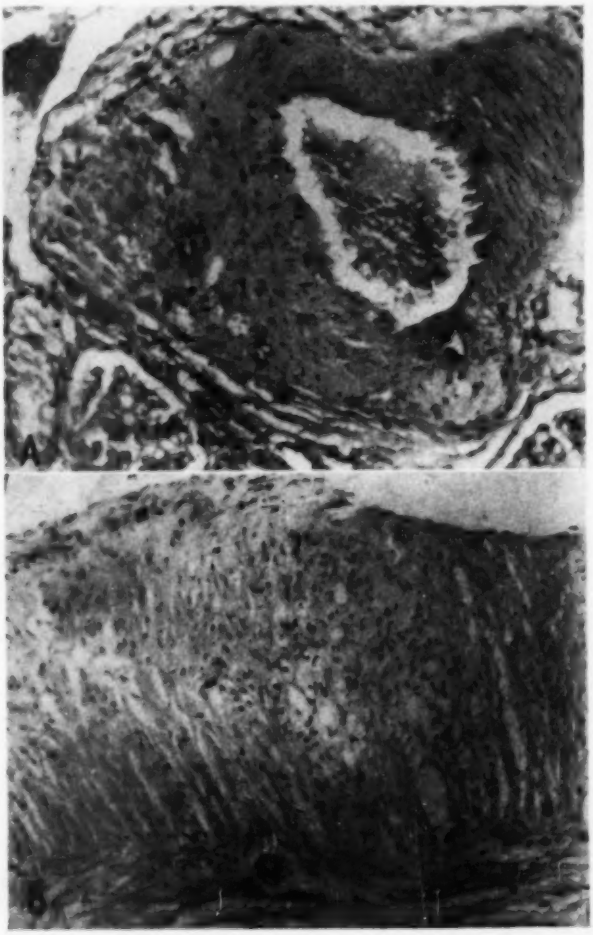

Fig. 10.—*A*, medium-sized artery (HT 50) showing foam cells in medial layer; × 160; hematoxylin and eosin. *B*, large abdominal aortic branch (HT 29) showing collection of foam cells in media; × 80; hematoxylin and eosin.

all instances these lesions of muscular arteries were similar, and they were identical with those observed in the coronary arteries.

The lumens of two of these vessels were completely occluded by massive intimal plaques. No thrombosis was demonstrated.

These lesions were characterized by huge collections of macrophages or foam cells, lying mainly in the medial and intimal layers. In some vessels these groups of cells were found only in the media (Fig. 10 *B*). With enlargement of the groups of foam cells, the overlying internal elastic membrane became fragmented or absent, and the lipide-containing cells extruded into the intima. In some instances the media had been completely replaced and the adventitia was also infiltrated with foam cells. In one instance this process resulted in adventitial fibrosis and infiltration with lymphocytes and plasma cells. Some of the foam cells were surrounded by delicate reticulum fibers. Condensed, coarse, collagenous fibers were found occasionally in the inner portions of the intimal plaques. The lesions also contained small amounts of mucoid material closely associated with the connective-tissue

TABLE 2.—*Diet and Blood Lipides of Hypophysectomized-Thyroidectomized Dogs*

		Diet Fed Daily*					Period Observed After HT		Body Weight, Kg.		Total Blood Lipides at Time of Death,† Mg. per 100 Ml.
Dog No.	Sex	Meat, Gm./Kg.	Sucrose, Gm.	Raw Pancreas, Gm.	Choline, Gm.	Methionine, Gm.	Yr.	D.	Initial	Final	
HT 6	F	30	50	..	..	..	1	54	8.0	16.5	887
HT 10	F	30	50	..	..	..	1	33	8.6	20.6	821
HT 18	M	30	50	..	..	..	..	122	10.2	18.0	1,030
HT 21	F	30	50	..	..	..	..	217	7.9	14.5	1,133
HT 22	F	30	50	..	..	..	..	311	8.5	19.7	922
HT 47	F	30	50	..	..	..	2	19	6.5	8.0	946
HT 49	F	30	50	..	..	..	2	19	7.0	8.5	782
HT 34	F	30	50	25	..	..	2	96	7.5	9.2	798
HT 37	F	30	50	25	..	..	2	96	6.3	9.2	1,049
HT 38	F	30	50	25	..	..	2	91	5.5	7.0	772
HT 45	F	30	50	25	..	..	..	198	7.1	6.2	582‡
HT 48	F	30	50	25	..	..	2	19	7.0	11.7	945
HT 50	F	30	50	25	..	..	2	19	6.5	15.0	2,465
HT 28	M	30	50	..	2	..	2	52	5.6	9.0	2,491
HT 29	M	30	50	..	2	..	2	52	9.4	14.2	4,732
HT 30	M	30	50	..	2	..	2	52	6.2	11.1	1,068
HT 31	M	30	50	..	2	..	1	355	6.9	8.1	1,273
HT 33	F	30	50	..	2	..	1	355	6.0	10.8	1,290
HT 40	M	30	50	..	..	4	2	82	8.0	10.7	1,430
HT 41	F	30	50	..	..	4	2	92	6.0	8.8	1,346
HT 42	M	30	50	..	..	4	2	92	8.7	16.7	2,154

* The amounts of meat were based on the initial weight of the dog.
† Sum of total fatty acids and total cholesterol
‡ Animal ill.

structures. Little of this mucoid substance was removed by treatment of the sections with testicular hyaluronidase.

Lipide material was found in abundance in vacuolated muscular cells of the media as well as in macrophages. It stained pale pink with Nile blue, and only minimal amounts of refractile material were found in sections examined with polarized light.

It is of interest to note that the pronounced vacuolation of the muscular cells of the media of atherosclerotic aortic branches in two dogs stopped abruptly at the junction with the muscular media of the abdominal aorta.

3. CHEMICAL FINDINGS

The total lipide content of the plasma of the 21 HT dogs was determined at the time of killing. The values, which with a single exception ranged from 772 to 4,732 mg. per 100 ml., were considerably higher than those observed in our normal dogs. The preoperative values for the 21 dogs ranged from 400 to 600 mg. per 100 ml.

With the exception of HT 45, all dogs showed significant increases in body weight after the second operation. This increase was taken as evidence of adequate nutrition throughout the experiment.

COMMENT

Two types of arterial disease were observed in our HT dogs, the first fundamentally fibrous in origin and the second primarily lipide in origin. The former was found mainly in the aorta, whereas the lipide type was found more often in the coronary and other medium-sized, muscular arteries.

The aortic intimal lesions in the HT dogs, like those of normal dogs,[6] were characterized by an early degeneration of the internal elastic membrane associated with deposition of mucoid substance. This was followed by proliferation of fibrous tissue. In the earlier, smaller lesions, lipides were not demonstrable. The progressive rearrangement of the intimal connective tissue and secondary changes, including hyalinization and cartilaginous metaplasia, observed in these dogs were identical with those previously reported in normal old dogs.[6] The intimal plaques in the aortas of the HT dogs were in all but one instance smaller than those observed in normal old dogs. These plaques consisted mainly of amorphous or fibrillary mucoid substance and showed relatively little collagenous replacement. The degree of development of these intimal plaques was comparable to that of normal, younger dogs previously described.[6]

Lipide infiltration in these aortic intimal plaques of the dog follows the fibrous proliferation. In normal dogs, lipide infiltration is minimal, but its incidence is higher in old dogs than in younger ones. In the HT dogs, the lipide infiltration of the intimal plaques was more extensive. Whereas the intimal plaques of normal dogs are gray or white, those of the HT dogs were often yellow, indicating the presence of fat. Small amounts of lipides, visible with polarized light, were occasionally observed in the aortic lesions of the HT dogs, while in normal dogs no refractile substance was present. Lipide infiltration in the medial layer in normal dogs was found only adjacent to lipide-infiltrated intimal plaques,[6] whereas among the HT dogs medial lipide infiltration without other aortic disease was observed in 9 of the 21 animals. The pattern of intimal alteration by the lipides, however, was similar in normal and in HT dogs. In addition to the presence of fat in the intimal connective-tissue cells and in the intercellular spaces, lipide was observed in macrophages in the intima of three dogs.

The second type of arterial lesion observed in HT dogs is primarily lipide in origin. In the large and medium-sized coronary arteries, in the renal and hepatic arteries, and in branches of the aorta, there were vascular lesions characterized by lipide infiltration of the intimal or medial layers or both, without evidence of previous fibrous intimal disease. The lipide infiltration and deposition were followed by the formation of foam-cell plaques which were often large enough to occlude substantially the vascular lumens and extensive enough to distort or even partially destroy the internal elastic membrane, the media, or both. These vascular lesions closely resembled spontaneously occurring foam-cell lesions described by Bloom.[7] The appearance of mucoid substances and connective tissue in these arterial lesions of HT dogs was clearly a reaction secondary to the lipide deposits. As in the aortic

7. Bloom, F.: Am. J. Path. **22**:519, 1946.

lesions in these dogs, little refractile material could be demonstrated with polarized light, even in arteries with an abundance of lipide substance.

It should be noted that some of the coronary arterial lesions of the HT dogs were identical with those observed in normal dogs. These were characterized by intimal fibrosis or medial hypertrophy; lipides were absent in these coronary lesions. This was the case in only 3 of our 21 HT dogs, whereas 6 of them showed the coronary lesion which we have described as lipide in origin.

There appeared to be no significant correlation between terminal plasma-lipide levels and the degree of lipide infiltration of the vessels of the HT dogs. The lipide levels of the HT dogs as a group were higher than those of normal dogs, and the amounts of lipide in the vascular walls were also significantly greater in the HT dogs than in the normal ones. It is significant that the feeding of raw pancreas or choline or methionine did not appear to influence the character or degree of lipide infiltration in the arteries of our HT dogs.

SUMMARY

The present report is based on a study of 21 dogs, most of which were killed about two years after removal of both the thyroid and the pituitary gland.

These dogs had high levels of plasma lipides even though they were fed a diet consisting mainly of lean horse meat and sugar.

Two basic types of vascular lesions were observed: 1. In the aorta and to a lesser extent in the coronary arteries, the earliest lesion was an alteration of the internal elastic membrane associated with intimal deposition of mucopolysaccharide and collagen. This lesion was identical with that previously observed in normal dogs; secondary lipide infiltration of the intima of the aorta was, however, more pronounced in the HT dogs than in normal dogs. 2. In the medium-sized arteries, mainly coronaries, there were lesions characterized by a primary deposition of lipide in the intima or media, followed by fibrosis. Similar lipide lesions were seen in the cardiac valves. In the aortas of 9 of the 21 dogs lipide infiltration of the media without other medial or intimal disease was also observed.

In the HT dogs small amounts of refractile material (presumably cholesterol) were found in some vascular lesions containing other lipides; in the vascular lesions of normal dogs this substance was not identified.

The daily feeding of either 2 gm. of choline chloride or 4 gm. of methionine did not appear to influence the extent of the cardiovascular lesions in the HT dogs.

News and Comment

Wisconsin Society of Pathologists.—At the meeting of the Wisconsin Society of Pathologists on Oct. 7, 1952, the following officers were elected:

President—Edward A. Birge, Milwaukee

Vice-President—John B. Miale, Marshfield

Secretary-Treasurer—Robert S. Haukohl, Milwaukee

Board of Censors—D. Murray Angevine, Chairman, Madison
Etheldred L. Schafer, Madison
Walter H. Jaeschke, Madison

Counselor of the ASCP—S. B. Pessin, Milwaukee

The scientific portion of the meeting consisted of a round-table discussion led by Dr. Paul R. Cannon, of Chicago, on "Electrolyte Metabolism."

Jean Oliver Awarded William Wood Gerhard Medal.—Jean Oliver, Professor of Pathology in the State University of New York College of Medicine in New York City, Brooklyn, was awarded the William Wood Gerhard Medal for "Zeal in Research" at the meeting of the Philadelphia Pathological Society on Nov. 13. Dr. Oliver addressed the meeting on Correlations of Structure and Function and Mechanism of Recovery in Acute Renal Failure.

The Gerhard Medal was established in 1925 by the Society in honor of Dr. William Wood Gerhard, its first President, in 1838, and is awarded at occasional intervals to workers in the field of pathology. Previous recipients have been William Welch, Theobold Smith, F. d'Herrelle, Eugene Opie, Simon Flexner, A. N. Richards, George Whipple, Frank Mann, Warren and Margaret Lewis, and Paul Cannon.

American Association of Blood Banks.—The Fifth Annual Meeting of the American Association of Blood Banks was held in Milwaukee, Oct. 9-11, 1952. Israel Davidsohn, M.D., of Chicago was inducted as President for 1952-1953. Other officers elected were Aaron Kellner, M.D., of New York, President-Elect; Merlin L. Trumbull, M.D., of Memphis, Vice-President; Mrs. Bernice Hemphill, of San Francisco, Treasurer, and Miss Marjorie Saunders of Dallas, Texas, Secretary. The Sixth Annual Meeting of the Assocation will be held in Chicago, Oct. 17-20, 1953, at the La Salle Hotel.

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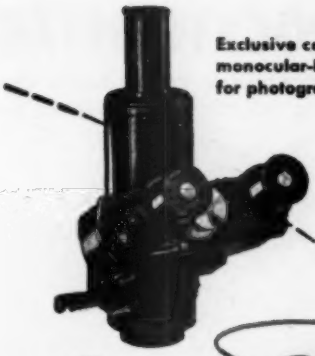

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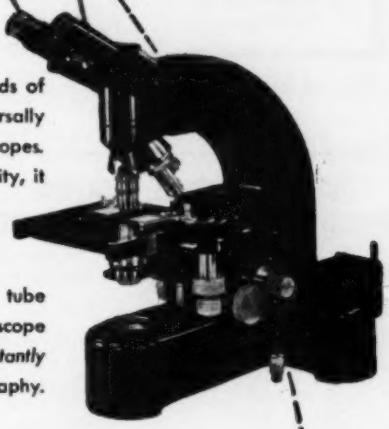

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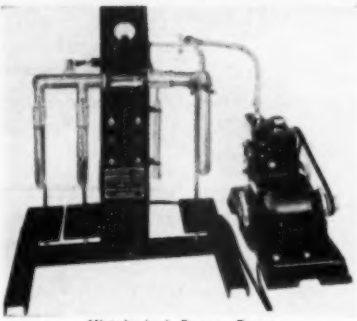

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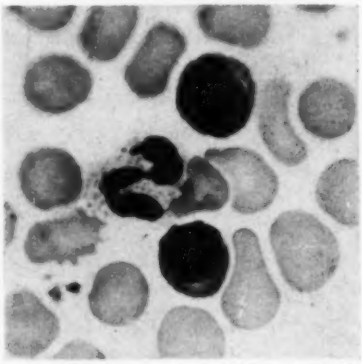

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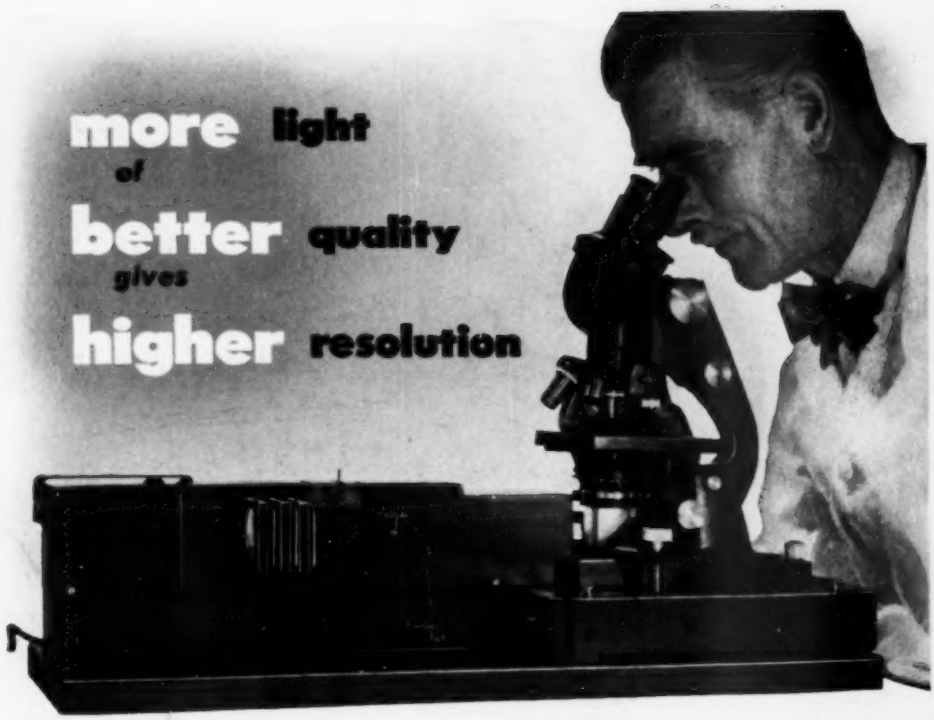

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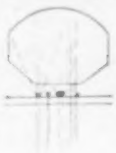

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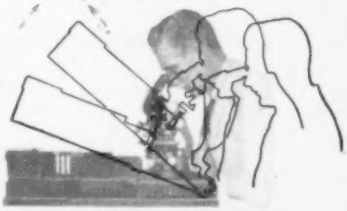

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